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THE BRITISH JOURNAL OF TUBERCULOSIS AND DISEASES OF THE CHEST

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BRITISH JOURNAL OF TUBERCULOSIS AND DISEASES OF THE CHEST

Vol. XLIX. JANUARY, 1955 No. 1.

EDITORIAL

THE year 1954, readers will recall, saw a number of changes in the format of the Journal, commensurate with its expanding influence and widening sphere of activity, resulting in increased circulation in Great Britain, the Dominions, the United States, Europe and Asia.

The approval with which these changes have been received has, not unnaturally, been a matter of satisfaction to the Editorial Board and the Publishers. With the advent next year of our Golden Jubilee it is hoped that this Journal, the oldest of its kind, will become still more influential in the medicine of the future, with particular reference to the Tuberculosis and Chest Service in Great Britain.

The organization of the future Chest Service and its status in the National Health Service, which is now established as a permanent feature of the social and economic structure of this country, is a matter of great concern to us all. It is now generally recognised that a complete service will have to embrace all aspects, medical and social, of chest work, including tuberculosis, and that the out-patient Chest Clinics, linked with Mass Radiography units, and the In-patient regionalised Chest Units and Hospitals (formerly sanatoria) shall all be linked to the General Hospital Service.

The need for broadening the former exclusively Tuberculosis Service to one that incorporates all Chest Services has now, in the main, achieved widespread recognition. Cancer of the lung, industrial lung disease, chronic bronchitis and emphysema, bronchiectasis, the pneumonias, the common cold, influenza, etc., all bring in their train social and economic as well as medical problems. Attention to these must, however, in no way be allowed to detract from the problem of tuberculosis, whose incidence, despite a falling mortality rate, gives no cause for complacency. The war against pulmonary tuberculosis must enlist every member of the community. It must also be borne in mind that the remarkable advances in chemotherapy can also give rise to more problems than they solve.

One thing is incontrovertible: the social aspects of chest disease cannot be divorced from the clinical, and future planning will yield a high dividend from co-ordinating the general practitioner, local authority and hospital services rather than by prolonging the existing tripartite service. Such a move will help to overcome the criticisms or deficiencies of the National Health Service, inevitable in the first few years after its inception, and to avoid excessive concentration on individual illness at hospital level at the expense of the wider

consideration of the health of the nation. In the words of the late John Ryle: "The whole man and his family must become the concern of the practising physician," and medical education and research must devote its energies to achieving this object. The physician with specialised leanings towards chest disease must concern himself with the natural history, causation, prevention, diagnosis, changing pattern and treatment of diseases such as bronchitis, emphysema, industrial lung disease, asthma, bronchiectasis, as well as conditions of cancer and tuberculosis, for each and all of these are responsible for varying degrees of morbidity, mortality and socio-economic stress.

We must, for example, never forget the lessons of the 1952 fog as it affected the chronic bronchitic;* it is also significant to compare the death rates for England and Wales for lung cancer 1953 (15,128) and respiratory tuberculosis (7,913), which show approximately two deaths from cancer to one from tuberculosis. Furthermore, a study of the death rates for respiratory tuberculosis, lung cancer, pneumonia, bronchitis and other diseases of the respiratory system illustrates the diminishing tuberculosis rate and increasing rates in some of these other conditions. Factors of heredity, environment, hygiene in home and factory, standard of living, including housing and nutrition, and the elimination of harmful dusts and fumes in industry, must all be our concern. The price of prevention of many such diseases is infinitesimal by comparison with the high cost of treating an established case.

We would maintain, therefore, that although an investigation of these factors is less dramatic than, for example, the administration of antibiotics in acute or chronic pulmonary diseases, it is no less important. Future trends must, therefore, integrate social and clinical medicine and regard causation, prevention, diagnosis, treatment and after-care as one continuous process.

Ever mindful of changing patterns in certain contemporary chest diseases, it will be the concern of this Journal to publish, alongside the established original clinical and pathological contribution, others which have investigated etiological, social, psychological (stress and strain), industrial and nutritional, etc., factors in disease. The application to chest disease of the epidemiological techniques must also engage our attention.

Such then, in brief outline, is something of our programme for the future.

P. E.

* In this connection, the Beaver Report, advocating legislation to reduce the amount of air pollution in Britain's towns and cities is worthy of the closest scrutiny.

THE CONTROL OF PULMONARY TUBERCULOSIS IN A GROUP OF INDUSTRIAL ESTABLISHMENTS

By G. F. Keatinge

From the Medical Department of the Butterley Group, Ripley, Derby, and of George Edwards and Sons, Hosiery Manufacturers, Somercotes, Derby

In a recent study in Northamptonshire boot and shoe factories (Stewart and Hughes, 1951) it is claimed that in about 40 per cent. of the cases of tuberculosis occurring amongst workers in these factories the actual infection took place within the factory, while it was estimated that home contact with the disease was responsible for not more than 25 per cent. of the same total. The validity of these conclusions is by no means universally accepted, but in the course of comment on them in a leading article in the *British Medical Journal* (1952) the importance of measures to control tuberculous infection in industry was presented as a "formidable challenge to the guardians of industrial health," and one of the writer's suggestions was that care should be taken to eliminate sources of infection at the place of work.

This is surely a counsel of perfection, but it may not be impossible to keep unknown and uncontrolled sources of infection at a low level, and in this article an account is given of an attempt to do so in a group of works, factories and quarries in Derbyshire, Nottinghamshire and Leicestershire.

There were eighteen units in this group, which comprised:

Type of Unit	*No. of employees*		*Total*
	Male	*Female*	
An iron foundry	241	4	245
An engineering machine shop	109	2	111
A constructional engineering shop, where the fabrication of bridges and cranes is undertaken	230	1	231
An iron rolling mill	266	10	276
A railway wagon building and repair shop	230	18	248
A shop for the manufacture of agricultural machinery	19	1	20
A shop devoted to the repair and maintenance of civil engineering plant	95	—	95
Four brickworks	240	8	248
Two quarries	52	4	56
A shop for the manufacture of precast concrete slabs, kerbs, etc.	30	—	30
A hosiery factory, making nylon stockings	119	176	295
Market gardens	7	3	10
An estates maintenance department	60	—	60
A farm of 2,065 acres	75	6	81
The central offices, including the drawing offices, of a large industrial company	82	99	181
Total	1,855	332	2,187

(*Received for publication August* 18, 1954.)

The total number of people employed from 1947 to 1953 inclusive has not varied greatly, and it will be seen that at the present time there are 2,187 workers in this group, which consists of 1,855 men and 332 women. It is the policy in all these industrial units to employ tuberculous patients if this can be done without involving danger to themselves or their fellows.

New Entrants

Since 1947 all new entrants have been submitted to a comprehensive placement medical examination, including routine radiography of the chest, and during the seven years under review 3,421 persons have been examined, of whom 2,861 were men and 560 were women. All people showing doubtful appearances in the X-ray film of chest or other evidence of active pulmonary disease have been referred to the chest physician through the general practitioner for confirmation of diagnosis and treatment. Eight cases of proved active pulmonary tuberculosis were discovered, giving a rate of 2·5 per thousand. This is somewhat lower than the national figure of 3·3 per thousand recorded in Mass Miniature Radiography Surveys (Ministry of Health, 1954).

Male

Age Groups:	15-25	26-35	36-45	46-55	55+	*Total*
Number of male new entrants examined	1,290	777	411	250	133	2,861
Percentage to the nearest whole number	(45%)	(27%)	(14%)	(8%)	(4%)	(98%)
Number of active cases of pulmonary tuberculosis	3	2	—	2	—	7
Number of quiescent cases of monary tuberculosis	1	7	2	2	1	13

Female

Age Groups:	15-25	26-35	36-45	46-55	55+	*Total*
Number of female new entrants examined	419	67	38	26	10	560
Percentage to the nearest whole number	(75%)	(12%)	(7%)	(4%)	(2%)	(100%)
Number of active cases of pulmonary tuberculosis	—	1	—	—	—	1
Number of quiescent cases of pulmonary tuberculosis ..	—	1	—	—	—	1

Male and Female

Age Groups:	15-25	26-35	36-45	46-55	55+	*Total*
Total number of new entrants examined	1,709 (50%)	844 (25%)	449 (13%)	276 (8%)	143 (4%)	3,421 (100%)

The Table gives the number of new entrants by sex and age group. It will be noted that the great majority of people were under the age of 36 and almost three-quarters of the women were in the age group 15-25, in which tuberculosis of the lungs is so liable to develop. Nevertheless, of all the female new entrants only one case of active respiratory tuberculosis was discovered and that was an early lesion in a young married woman aged 30 years. There were seven cases of active pulmonary tuberculosis amongst male newcomers; five of these men were in their twenties and the remaining two subjects were aged 48 and 53 respectively. In only one of these people who were discovered to be suffering from active tuberculosis had the disease been previously suspected, and this was in the case of a man aged 53 years who had been under treatment in a sanatorium for tuberculosis of the left lung fourteen years earlier, and had been subjected to phrenic interruption. There was at the time of examination an extensive recrudescence of activity in the left lower lobe. In three cases the men had been discharged fit on demobilisation from the armed forces a short time previously, and two of them had spent several years on active service in the Middle East and the Mediterranean theatres of war.

The possibility of home contact was investigated in every case, but evidence was only found in one instance, that of a young man of 25 years of age, living with his wife and two small children in overcrowded conditions as lodgers in the house of a tuberculous landlord.

In eight other cases—all men—anomalous X-ray appearances were seen, but investigation showed them to have either non-tuberculous or quiescent lesions; there were also six cases of known quiescent pulmonary tuberculosis, one a woman, and all these people were placed in jobs in consultation with the chest physician. Suitable work for such people is by no means always easy to arrange, for clearly much depends on intelligence, previous education and training. However, three were qualified to undertake office work which can certainly be regarded as suitable employment for the quiescent tuberculous patient. Of the eleven others, all of whom were men, one was given work as a gardener, and another as an assistant storekeeper, but the remainder were placed in selected labouring jobs. It may be held that the person who has a quiescent tuberculous lesion is unfitted to work as a labourer, but it must be emphasised that the placing possibilities and indeed the choice of employment in those lacking special skills are limited. Moreover, the term " labourer " is a wide one and the work done may not necessarily be unduly strenuous; however, a criterion by which the suitability of the work allotted to these people may be judged is the fact that all of them are still working for the Group and are in good health, save one in whom renewed activity has occurred. This took place in a man of 28 years of age who had been in hospital from July 1950 to January 1952, and on starting work in June 1952 an artificial pneumothorax was still being maintained by fortnightly refills. He was, accordingly, under frequent supervision by the chest physician and in August 1953 the disease had improved to such an extent that the lung was allowed to re-expand; however, four months later his condition had deteriorated, the sputum had become positive, and it was decided to re-admit him to hospital for thoracoplasty.

Three of the men discovered at entry to be suffering from active respiratory tuberculosis were also subsequently placed in work after the disease had become

quiescent following treatment. Two of the three were skilled workmen and were returned to their trade as fitters. The third man was a semi-skilled operator, a driller, who was considered capable of work of this kind.

An attempt is always made to keep in touch with those in whom active tuberculosis is recognised at entry and to follow their fortunes. Co-operation on the part of these people is remarkably good and it is surprising to find the strength of the doctor-patient relationship even following so impersonal a procedure as an examination on behalf of an industrial firm. Close liaison is maintained with the chest physician in keeping under constant review the health of people who have quiescent tuberculous lesions, and indeed the health of all workers is carefully supervised.

Established Workers

There is always the chance that pulmonary tuberculosis will arise in established employees, but it is not possible to impose routine radiography of the chest on people already in the factory, and it was considered that to try to carry out a necessarily incomplete survey by voluntary means would be an unwise policy, likely to defeat its object, even if for other reasons thought desirable. No attempt has therefore been made to undertake routine X-ray surveys of the chests of employees except in the case of those in the foundries, who are the only workers in the group exposed to an undue risk of pneumoconiosis. However, an attempt is made to supervise carefully the health of all workers and considerable reliance has been placed on keeping a careful record of sickness absence. All those suffering from prolonged absence or repeated short absence due to illness have been interviewed on return to work and, if indicated, examined and the chest X-rayed. Particular attention is naturally given to respiratory illnesses, but vague complaints not satisfactorily explained are also investigated.

In addition, young people up to the age of 18 years are seen at three-monthly intervals and are subsequently interviewed yearly up to the age of 20. The height and weight are checked and a note is made of the general condition; the dental state and absence due to sickness or accident is reviewed. The adequacy of the diet is assessed and enquiry is made about social activities and recreations. All this evidence is considered on its merits and also in relation to the kind of work being undertaken. If for any reason the state of the young person is felt to be unsatisfactory such investigations as may be indicated are carried out, including X-ray of the chest where required. As a result of these measures nearly 70 per cent. of established workers throughout the group have been submitted to radiography of the chest at one time or another, and in the seven years under review three cases of active pulmonary tuberculosis amongst them have been brought to light and none through any agency other than that of the occupational health service of these industrial establishments. By these means pulmonary tuberculosis is controlled.

The first case was recognised early in 1947, when the clerk of works to the estates department reported that he had been feeling very much off colour; he had lost much weight in the previous month or two, and X-ray of the chest revealed extensive disease in the upper zone of the right lung field with infiltra-

tion also at the left apex. There was no home contact and the source of infection was not discovered. Treatment was unavailing and he gradually went downhill, dying just over a year later. The second case occurred in a young man of 20 years of age, an apprentice fitter in the wagon works who had been away from work in the early part of 1948 on two occasions, separated by only a short interval, and his illness had been certified as influenza. However, he looked ill, and on radiography of the chest much infiltration was present throughout the left lung with cavitation in the left upper zone. Enquiry showed that a brother with open pulmonary tuberculosis was living in the same house. Prompt reference to the chest physician followed by nearly two years in hospital, during which a thoracoplasty was performed, succeeded in bringing the disease under control, and after a course of re-training he returned to the company's service as a clerk in the early part of 1951. The third case was a driller, a man of 71 years of age, who complained in 1951 of cough, and on X-ray of chest the film showed some old, apparently well healed, lesions at the right apex. Serial X-rays showed no alteration in the X-ray findings. There was no source of infection in the home, but quite suddenly in 1953 he had an acute chest illness and began to deteriorate. X-ray of the chest now showed that extensive disease was present, involving the whole of the right lung with collapse of the lower lobe. This man is still alive and has improved to some extent on streptomycin and P.A.S. All the work contacts of these three men were X-rayed and no cases of tuberculous disease of lung, active or quiescent, were discovered.

Meanwhile, during the years covered by this report, namely from 1947 to 1953, the incidence of pulmonary tuberculosis in people over the age of 15 in the two local authority areas where the majority of the industrial establishments concerned are situated was no less than 6·4 cases per 1,000, or nearly three times greater than the incidence in the industrial group under review (Bingham and Bingham, 1947-53; Ryan, 1947-53).

Discussion

Home contact was definitely absent in the three cases of pulmonary tuberculosis discovered amongst established workers, and there was strong evidence against the idea that actual infection took place within the factory. Of the eight new entrants found to be suffering from the disease, home contact was present in only one case, and although a specially careful occupational history was taken from each person, no likely source of infection at work could be established in any instance. So far as this relatively small group of persons is concerned, therefore, it can be said that although there was nothing to suggest that infection took place in any case at work, there was on the other hand a clear history of home contact in only one person. The really disturbing feature is that in eleven out of twelve of the people found to be suffering with active pulmonary tuberculosis the source of the infection remains obscure. Of course, close contact takes place not only in the home or in the factory, but in other places such as the hotel bar, the cinema, the dance hall, and even amongst spectators at football matches. "The rabblement hooted and clapped their chapped hands and threw up their sweaty nightcaps and uttered such a deal of stinking breath," and with it the tubercle bacillus.

Summary

Measures to control the incidence of pulmonary tuberculosis in a group of twenty industrial establishments in Derbyshire, Nottinghamshire and Leicestershire, employing 2,187 persons, are reviewed.

Since 1942 it has been a condition of employment for all new entrants to be submitted to placement medical examination, including radiography of the chest.

3,488 new entrants have been examined: of these 2,923 were men and 565 were women. The new entrants are analysed by sex and age group.

Eight cases of proved active pulmonary tuberculosis were discovered amongst the new entrants. Only one case occurred in a woman aged 30 years. Five of the 7 men were in their twenties and the remaining 2 men were aged 48 and 53 respectively.

Fourteen cases of known or suspected quiescent tuberculosis of the lung, one a woman, were also encountered and placed in employment.

Problems of placement of the quiescent tuberculous patient are discussed. Only one case in this survey broke down.

Three men found at entry to be suffering from active tuberculosis have subsequently been placed in employment within the group after treatment had rendered the disease quiescent.

Close supervision of the health of all employees is maintained, but routine radiography of the chest is not generally practicable, and reliance is placed on X-ray of chest on indication.

Three cases of active tuberculosis of the lung have been discovered amongst established employees during the seven years under review. In the same period of time the incidence in the local authority areas in which the group of industrial establishments are situated was three times as great.

The possible sources of infection are discussed.

My grateful thanks are due to the members of the nursing staff who have undertaken much routine follow-up work and have also been largely responsible in conjunction with the management for carrying out decisions on the placement in work of persons whose disease was under control. It is a pleasure also to acknowledge the willing co-operation given at all times by the chest physicians and general practitioners, and I am indebted to my friends, especially Dr. A. I. G. McLaughlin, for much helpful advice and criticism.

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A CLINICAL APPRAISAL OF CYANACETIC ACID HYDRAZIDE IN CHRONIC PULMONARY TUBERCULOSIS

By Thomas Marmion

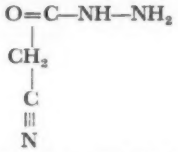
From the Sanatoria in Switzerland Treating British Ministry of Health Patients

Introduction

Cyanacetic acid hydrazide had been synthesised during the last century, but until 1952 when Valdecasas *et al.* reported upon its value in chronic pulmonary tuberculosis it had not been put to therapeutic use. The substance was then tested on the supposition that the substitution of the pyridine ring of isonicotinic acid hydrazide with an aliphatic chain would eliminate toxicity while maintaining those anti-bacillary characteristics due to a specific relative position of the linked nitrogen and the lateral chain: the crystallochemical similarity of the molecules of the two substances offers an explanation of their pharmacological affinity (Amorós and Coves, 1953). The published clinical work on cyanacetic acid hydrazide (Reazide,* Cyanazide, Hidacian, Armazal, CAH) has come from the Continent (Valdecasas *et al.*, 1952, 1953; Scheu, 1954; Sivrière, 1954; Riska, 1954). It has also been used in South America as a measure in the treatment of leprosy (Capurro and Wilkinson, 1954), and for asthma concomitant with tuberculosis (Quisumbing, 1953). De la Riva (1953) has reported on its action in cases of meningeal and cerebral tuberculosis. Its use against tuberculosis verrucosa has been noted by Vilanova and Valdecasas (1953). Results of *in vitro* and of experimental work have been reported from Switzerland by Hartl (1954) and discouraging reports have been given in England, in 1954, by Robson, Barnett *et al.*, Bavin and Seymour, and by Stewart and Wallace. However, studies made at the Ministry of Health Sanatoria at Davos, Switzerland, over the last six months have shown that clinically the drug is of a certain value in pulmonary tuberculosis, and while yet to be appraised with o-hydroxybenzal isonicotinyl hydrazone and 1-isonicotinyl-2-isopropyl hydrazine, it compares favourably with other isonicotinic acid derivatives and should hold a place in the treatment of this disease.

Pharmacology

The drug is a water-soluble substance with the formula



* "Reazide" used in this investigation was supplied through the courtesy of Laboratoires OM, Geneva.

(*Received for publication November* 16, 1954)

Sterilisation must be by filtration methods as the solutions are thermolabile.

Gordonoff (1953) gives the intraperitoneal LD_{50} for mice as 283·4 mgm./kg. (with INH the median lethal dose is 154·2 mgm./kg.); similar figures are found with rats. The minimum inhibitory concentration against a normal $H_{37}Rv$ strain in the case of CAH is 3μg./ml. (INH: 0·03μg./ml.). Corneal and survival tests with CAH have shown it to have but a poor protective action. These results demonstrate that CAH is not to be compared in bacteriostatic strength with INH, though its toxicity should be less. However, some workers, notably Arroyo (1953), have obtained different figures and believe that the drug has a considerable bacteriostatic power; again, in this present series the incidence of toxic reactions (of the same nature as those of isonicotinic acid) was higher in patients receiving CAH than in a comparable group having INH medication.

According to the first results obtained by Baudet (1954) the CAH blood levels seem to be clearly higher than those found for INH by other authors.

The dosage employed is between 5 and 10 mgm./kg. of body weight per day. It is given orally in divided doses. The course of treatment lasts from two to four months and depends, like other anti-tubercular agents, upon tolerance and the emergence of resistant organisms.

Clinical Material

Since March 1954, 31 patients have been treated with CAH, either alone or in combination with other drugs, at the Sanatorium Angleterre in Davos, Switzerland. The treatment in all cases was for pulmonary disease, though its effects on an attendant lupus vulgaris and on an asthmatic state were recorded.

These patients were all men and the disease in every instance was of a long standing. Most of these men with chronic tuberculosis were considered on radiological grounds to be cases of either slowly progressing disease or cases, clinically ill, in which serial radiographs had shown no change in disease extent. No early case of tuberculosis received the drug, and where another agent was thought, through previous experience, to be of a definite and proven value it was used in preference.

In this respect this work must be regarded as a " pilot " experiment and

Table I.—Type of Lesion*

Type of lesion	*Fibro-caseous*				*Fibrous*		
Type of lesion	*Advanced*		*Advanced with dissemination*	*Post-primary Tuberculoma and residual fibrotic*	*Chronic miliary*		*Fibro-cavitaria*
	Moderately advanced	*Advanced*			*Localised*	*Generalised*	
Number of cases	3	7	3	2	6	3	7

* The radiological terminology used in this article is that suggested by Sekulich (1953).

not as a comparative drug trial; and in assessing the results of treatment the material must be borne in mind. Again, this trial, like that of Riska (1954), cannot be regarded as ideal for the estimation of the drug's properties, for CAH was used at a disadvantage in that most of the patients had received large quantities of other antibacterial agents (by Continental standards); and such patients as were known sputum positive (10) had in the main (6) a known bacterial resistance to one or all of the other drugs.

All of these cases were of bilateral disease and most of them had had tuberculosis for a considerable time. Their period in Switzerland was as part of their convalescence, in preparation for surgery, or merely to give a change in different surroundings after a long time in one hospital. The length of time the patients had been in hospitals before receiving CAH, or under medical care at home and not working, is shown in Table II, as is the previous drug administration.

TABLE II.—PREVIOUS TREATMENT

Number of cases	*Previous duration of treatment*			*No drugs*	*Previous drug administration*						
					PAS, INH and SM	*Streptomycin*		*PAS*		*INH*	
	Under 1 year	*1 to 3 years*	*Over 3 years*		*Combined treatment of over 3 months*	*60 gm. or less*	*More than 60 gm.*	*6 months PAS daily or less*	*More than 6 months PAS daily*	*3 months INH daily or less*	*More than 3 months INH daily*
31	9	9	13	2	10	9	19	8	20	4	16

Only two cases had had no previous drugs before commencing on CAH; these were given a combined drug treatment. It will be noted that a third of the men had in the past streptomycin and PAS and INH, given together for over three months. In many cases well over 100 gm. of streptomycin had been given before admittance to this hospital.

Other measures than bed-rest and drug treatment had been employed in just over half of the cases. Thus a pneumoperitoneum had been tried in 6 cases, and was combined with a phrenic crush in a further case. One had had a phrenic crush without a pneumoperitoneum. An artificial pneumothorax was instituted during treatment with CAH in one man, but had to be abandoned because of extensive adherent sheets of pleural tissue; in three others this measure had been tried in the past. In one of these cases the pneumothorax was abandoned, it being thought to have served its purpose, and the other two bore the respective legacies of a bronchopleural fistula and of a frozen lung and fluid. [Other complications were: two of extensive tuberculous pleural involvement, one chronic asthmatic state, one post-nephrectomy, and one facial lupus). Four patients had had resectional surgery and one a thoracoplasty, the operations in every instance being of dubious value.

Clinical Method

When first using CAH it was given in 50 mgm. tablets three times a day for three days, and then increased by similar progression until the patient was receiving 8 mgm./kg. daily over three doses, one after each meal. Similarly, the drug was not stopped abruptly but gradually decreased in quantity. It was found that this did little to prevent toxic or secondary reactions and recently the full daily dose has been administered from the commencement of treatment.

While on this treatment the patients were kept on the low grades of a sanatorium regimen, being allowed up for toilet purposes and one meal a day.

At the time of this report 2 cases are still having CAH; of the 29 cases who have finished their treatment, 4 did not have a full course of the drug because of uncontrollable or persistent secondary effects, 5 received only two months' treatment, because it was judged to be sufficient, and the rest of the patients had a three-month course, with 4 cases going on to four, and 1 to five, months.

The majority of men in this series received CAH alone. Though known to be against the accepted teaching, that no anti-tubercular agent should be given by itself, it was thought that there were more advantages in giving the drug in this isolated and unaccepted fashion than by combining it with one which in all probability (and in fact with 6 of the positive cases) the bacteria had become resistant to over many months, or indeed years, of treatment. However, in the few instances where streptomycin or PAS had not been given before, or had been given only for a short while, or where the sensitivity was known, CAH was prescribed in combined therapy. These amounted to 4 cases of CAH and streptomycin, to 4 cases of CAH and PAS, and to 1 case of CAH plus streptomycin plus PAS, the PAS being given by the granulate or by daily intravenous infusions.

Radiographs were taken at monthly intervals. The sputum, blood and urine were investigated at the same time. A full clinical examination of the pulmonary and cardio-vascular systems was given every four weeks. For the first 20 patients in the series a total and differential corpuscular blood count was made at three-weekly intervals while they were receiving the drug, and monthly after its cessation, and until the patient's discharge. Though leucocyte counts were done the leucocytic nuclear variability (popular on the Continent as a prognostic index) was not noted as a matter of routine.

Results

Report on 29 Cases

Clinical.—No marked clinical change was seen throughout the trial. Four patients who volunteered that they felt " much better " were, in fact, radiologically improved. CAH did not affect the appetite. In the whole series there was nothing of import concerning weight change, temperature (no abnormal temperatures were charted during the six months, save from one patient who had a sensitivity to the drug), sputum quantity, or character of cough.

Those who had physical signs at the start of treatment still had the same signs when the drug was stopped. In view of the nature of the original disease

no great importance can be attached to this finding. No signs developed in any of the patients.

TABLE III

Erythrocyte Sedimentation Rate in mm. per Hour and per two Hours (Westergren)

Case No.	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*
Rate at start	58/80	37/72	35/61	15/34	13/32	10/29	10/26	9/27	8/18	7/17	6/16
After 1 month	47/82	9/30	6/16	8/20	13/36	25/48	7/20	6/16	5/15	6/17	4/15
After 2 months	33/62	12/31	2/4	16/38	5/19	12/35	7/20	3/12	2/5	2/7	5/12
After 3 months	40/75	4/14	1/3	8/21	4/14	3/9	1/4	3/10	2/3		5/14
After 4 months			1/5		3/9			4/13			5/11
After 5 months								5/17			

This table gives the serial readings of all patients who had an initial rate of over 5 mm. in the first hour. The other patients in the series kept their normal readings throughout treatment.

Twenty patients had a full cellular blood examination every three weeks for three months. The only finding that might be of importance was a rise in the polymorphonuclear leucocyte count of between 5 and 7 per cent. in 5 instances.

The hæmoglobin percentage and total blood cell counts did not significantly alter during CAH treatment. Clinical examination of the urine was normal at all times.

Of the 10 patients who were sputum positive at the start of treatment, two were found sputum negative on direct examination after three months. The others remained positive.

Side-effects.—Four cases had severe side-effects and a further 15 had minor reactions.

In the 4 cases that produced severe reactions the drug was stopped. One man was intolerant of all other drugs previously employed (PAS, INH, streptomycin). With CAH he developed a severe conjunctivitis and œdema of the para-ocular tissues. This occurred after three weeks on CAH and remained for six weeks after its withdrawal. Similar signs were seen with the other drugs, but they were not so prolonged in their duration. In the second case a distressing urticarial rash developed all over the patient's face, chest, abdomen and thighs. This came on after three weeks' treatment and lasted for a further week; on being put back on CAH the rash reappeared. The amount of CAH given in each case was only 3 mgm. per kilo per day. This patient had had long and intensive treatment with other drugs in the past without any cutaneous manifestations of intolerance.* The third patient was taken off treatment because he developed acute pain in the frontal region. These headaches

* A similar, though more serious and more extensive, reaction was given in another patient (not included in the trial, who received the drug after it had ended). The rash came on after 11 days and went, after stopping the drug, in 4. PAS, INH and streptomycin had been employed against the disease in large quantities without adverse effect. This further case is mentioned out of context as this side-effect is of considerable severity and is not generally recognised, though Biedermann (1954) mentions one instance where an urticaria caused CAH to be withdrawn from treatment.

lasted about half an hour, started on waking and after periods of rest; a mild pain " behind the eyes " was present throughout the day. At the same time he complained of lassitude and of palpitations. His blood pressure rose from 158/90 to 170/115. The symptoms came on at the end of a week's treatment, and stopped within two days of the drug being withdrawn. The blood pressure was 150/90 four weeks afterwards. This particular patient had had a left nephrectomy for a hydronephrosis of non-tuberculous origin six years previously—at no time was anything abnormal found in his urine or upon clinical examination other than what has been mentioned. The last patient who had CAH removed from his treatment suffered from a persistent paræsthesia in both legs. This was a common finding in the series, being reported from seven other patients, but it usually lasted only a few days, and was then present only for short or half-hourly periods. However, this man developed paræsthesiæ late on in his treatment, at the end of the sixth week, and it remained troublesome while he continued with CAH, for another two weeks.

Paræsthesiæ, commonly noticed in the legs and on the flexor surfaces of the fore-arms as " pins and needles," but also complained of as " tingling in the face," was noted in 7 other cases during the first week of treatment and bore no relationship to the dosage given.

Constipation was found in 4 patients, otherwise the gastro-intestinal system was not affected by CAH. Though constipation is a frequent attendant to bed-rest patients, it was here thought to be due to the drug, for, following its stoppage, the bowel was restored to normal action within a few days.

After one week's treatment 6 patients were seen to be tense, nervous and apprehensive. One of these was of an excitable nature but the others were not highly strung, rather the reverse. Phenobarbitone, ½ gr. twice daily, was needed to quieten one man, the other five stayed in this state of a mild euphoria while remaining on treatment. This was cut short to two months in two of them, because in addition a digital tremor became apparent after six weeks, and a further two stopped treatment because of the severe reactions noted above.

TABLE IV.—RADIOGRAPHIC ASSESSMENT

Type of disease	*Treatment*	*Number of cases*	*Radiographic report*			
			Improvement		*No change*	*Worse*
			Slight	*Marked*		
Fibro-caseous	CAH only	12	4	2	5	1
	CAH plus SM	2	1	1		
	CAH plus PAS ..	1			1	
Fibrous	CAH only	8	4		3	1
	CAH plus SM	2		1	1	
	CAH plus PAS ..	3	1		2	
	CAH plus SM and PAS	1		1		
TOTAL		29	10	5	12	2

Radiological.—The criteria for noting radiographic change was a diminution in the size of part, or of all, of the disease area; or an alteration in its character.

While some of the cases reported upon as slightly improved may have reached that state through the normal involutive process of the disease, the markedly improved cases, though few in number, showed radiographic clearing of a degree not normally seen after three months on a low-grade sanatorium régime only.

The specific changes in the markedly improved group were those of complete cavity closure in 2 cases and pronounced fibrotic change over all lung fields in the 3 cases of advanced fibro-caseous disease with dissemination: two of these also showed a reduction in the extent of the more recent disease, and one showed also a partial cavity closure.

Two cases were reported worse. This was on account of a slight extension of disease in one instance, and in the other to the appearance of a cavity (after four months on CAH) in a lesion previously confirmed as solid by tomography. Save for this latter case, it was noticeable that the definite radiographic changes were found at the end of the second month of treatment.

Discussion

In the small series of cases reported upon by Scheu in early 1954 there was a noticeable improvement in the general state of the patients while on CAH treatment. This was not dramatic and sudden (as were so many of the results claimed for INH in its initial trials) but gradual. In the main it was seen in weight increase and by the gradual disappearance of the toxic symptoms associated with tuberculosis. A later trial on a larger number of patients made by Riska in Finland (1954) was more unfavourable in its report, and put doubt on the statement, so often quoted after a few weeks' treatment, that the patient had now "a feeling of wellbeing." In the trial of any new drug, and especially if it is used on patients with chronic tuberculosis who have suffered long in hospital, one must beware of what de Cara (1952) has called "The Magic Phase." Again, when trying out a new agent the patient is repeatedly asked "Do you feel better?" and an answer is expected. That answer often depends on a whim of the moment. It is of some interest to note that during this trial this question was put weekly to patients not on any drug and the answer was yes more often than otherwise; yet if they had been part of a trial a minor but all the same inaccurate claim could have been made. No patient in this series knew that he was receiving a new drug; it was supposed that what they were having was INH, or yeast, or a new preparation of PAS. Undoubtedly this want of miracle drug suggestion was responsible for the absence of pronounced excitability and of subjective outbursts. While this confirms Riska's work (1954), it must be remembered that the cases in both these trials were similar, being of long standing, treated but not arrested, fibrous disease. On the other hand, Scheu (1954) observed patients who were of an earlier type of disease and who had not received beforehand intensive medication.

One of the most noticeable results of this CAH treatment was the rapid fall of the erythrocyte sedimentation rates. Cases A, B, D and F had a high

rate for many months before treatment started. In case B it had been above 30/50 mm. for at least two years, and in case F above 10/20 mm. for four years. All the other cases listed in Table III had had an abnormal reading on three instances taken at monthly intervals before treatment started. Because of this, the fall cannot be ascribed to bed-rest alone, and cannot be due to the action of a drug combination: for though three of these men had streptomycin with CAH and a further one had PAS, they were not unacquainted with these other drugs, and previous treatment had not altered the rate to the extent that was so pronounced while they were having CAH. This finding has been consistently commented upon in the published work on CAH. However, other clinicians have found that the rate, where initially above 25 mm. in the first hour, though reduced, rarely returned to within normal limits. (Floriani *et al.*, 1954; Riska, 1954; and Felber *et al.*, 1954). In our series, save in one instance, a normal reading was obtained at the end of treatment irrespective of the initial rate. It may be that the easily achieved and high CAH blood concentration affects rouleaux formation and the physics of cellular sedimentation; for though there is no doubt that the drug does alter the speed of sedimentation there is no firm correlation between that fact and general clinical improvement.

The complications that were met with were no new aspect of CAH treatment, for all previous clinical work has instanced them, and in about the same proportion: a little over one-third of all patients treated. Paræsthesiæ are the most commonly commented upon, a tingling sensation or soreness in the legs during the first few weeks of treatment. This usually disappears within days, but may occasionally be so severe as to warrant stopping the drug. Indeed, 5 of the 47 patients treated by Riska had treatment suspended because of this complaint. This latter trial also took into account the blood chemistry. Seven cases had a transient fall of the plasma cholesterol. No other abnormal biochemical changes have been reported. The cellular picture has also been found normal after months of CAH medication in all of the earlier work, the alteration in the white cell count being noted only in the present and Riska's series: little importance is attached to this finding.

Mild excitability is another side-effect frequently commented upon in all trials. It is perhaps better described as a state of apprehension, and can be easily controlled by barbiturates.

Riska has recorded 10 cases of vertigo occurring at the higher doses of CAH (8–10 mgm./kilo/body weight); this complaint was also given by Felber (1954) and by Kirshner (1954).

Other side-effects not met with in our series are microscopic hæmaturia, gastric hyperacidity, and sweating (Felber). Kirshner at the Laennec Society meeting in Philadelphia in 1954 also commented upon the appearance of a toxic psychosis, but it is probable that this was more a disturbance of an existing state than a direct action of CAH. This isolated case is of some importance in view of the similar psychotic manifestations that are known to follow INH therapy (Conrad and Schreib, 1953). Temporary loss of memory occurred in one of Felber's cases and two of Riska's patients also suffered from a disturbance of memory.

These side-effects are commented upon in some detail because, though the

drug is reasonably well tolerated, its secondary reactions are more numerous, and seem to occur more frequently, than those of INH, but they are rarely of grave import and in those instances where the patient has been taken off treatment it has been so more because of their continuance than because of their severity. From all the published reports it can be said that the main side-effects in order of frequency are: paræsthesiæ, excitability, and headache. No drug fevers have been seen and there have been very few patients who developed gastro-intestinal troubles. Only 3 cases of skin rashes are reported, one of which was in an allergic subject.

Quite definite improvement, and improvement that was not expected, was found in the serial radiographs of 5 of our patients, and a slight improvement was read from 10 films. It has already been said that this change was not one of time and rest only; this bears repetition; for the radiographic improvement seen after CAH treatment (in about half the cases) is one of the most noticeable findings to come from all of the trials. Well over half of Felber's patients gave this improvement on radiography. Anguera's paper (1954) is interesting in that it shows this change in patients whose major presenting complaint was hæmorrhage. Scheu has reproduced the plates in his paper as also has Floriani. Even in Riska's series there was an improvement in 12 out of 28 cases: though this included one instance of cavity closure, the change was in the majority of cases slight. But however slight, change of any degree for the better must be regarded as an advantage, and a considerable one when it is remembered that these patients had had the disease for a long while, and had received during that time other intensive drug courses.

In the past CAH has been used against diseases other than pulmonary tuberculosis; to these cases can be added two further ones. One man had an associated asthma. Breathing was made much easier after a month on CAH; he lost the pronounced dyspnœa on exertion that had previously embarrassed him. De Bustamente (1952) has recorded the case history of a woman who had an asthmatic crisis every four days before treatment with CAH, and Quisumbing (1953) comments favourably upon its value in abolishing the status asthmaticus in tubercular patients. Vilanova and Valdecasas (1953) describe the successful treatment of a woman with tuberculous verrucosa of the wrist with CAH. Histological comparisons with the known results of INH treatment showed that the essential difference was that there was no marked perifollicular fibrosis with CAH. One of our patients had an extensive lupus vulgaris. He was treated with CAH for his pulmonary disease, but after one month it was noticed that the facial complaint had completely altered in character. Its size was reduced, its colour more near that of normal skin, and the surface of the lesion was now smooth. Though these are very isolated reports the further study of CAH against lupus and the tuberculides would be of value. In this respect it is of interest to recall that some of the lesions of Hansen's disease benefit from this hydrazide (Capurro and Wilkinson, 1954).

The primary report of Valdecasas *et al.* in 1952 emphasised the importance of the non-emergence of resistant bacteria; for none were observed by them and at the time it was hoped that resistance to CAH would not occur. Unfortunately, this is now well recognised, and the point of debate is not its occurrence but whether bacteria resistant to INH are *per se* resistant to CAH. Barnett *et*

al. (1954) believe that isoniazid-resistant strains of *M. tuberculosis* usually show an increased resistance to CAH. This was also found by Stewart and Wallace (1954); and Bavin and Seymour (1954) believe that CAH has little activity against an INH-resistant organism. To a certain extent only the English observations confirm the findings of Oker-Blom and Riska (1954) in that there can be a cross-resistance and that the inhibitory power of CAH is less than that of the parent hydrazide. But this cross-resistance was found in only a small number of strains and the conclusions of the authors are that there is no clearly demonstrable agreement between the sensitivities of cultures to INH and CAH.

Nevertheless Hartl earlier in the year concluded that "Reazide has a distinct tuberculastatic effect *in vitro* against . . . INH and streptomycin-resistant strains" and radiological improvement has been seen in this present trial in patients who before treatment produced INH-resistant bacteria.

Again, a preliminary report from America (Kirshner, 1954) indicates that the drug may be of value in INH-resistant cases, and that bacteria found resistant to INH were not resistant to CAH. A further point of interest in this latter work is that bacteria from one patient who had had no drugs beforehand were found to be resistant to CAH. Much of the confusion may be due to cultural methods, for with CAH the laboratory findings vary widely with the media used. As the English work has emphasised, more work must be done before this question of shared resistance is fully understood.

Though some of the previous reports may have been over-generous in their eulogy, there is no doubt that CAH will be a useful drug for patients unable to tolerate INH (Gibson, 1954), and will be of considerable value in the treatment of chronic tuberculosis.

Summary

Thirty-one patients received cyanacetic acid hydrazide for periods of up to five months. Side-effects were common, four cases were taken off treatment. Clinical improvement was not marked. The erythrocyte sedimentation rate was reduced in all cases save one to within normal limits. Radiographic improvement was marked in 5 cases and present in 10. In view of the nature of the disease, and its course before treatment, this is considered to be of significance.

These results confirm previous work, though clinical improvement was seen more often in Continental studies.

Continental, American and English workers have given different reports concerning cross-resistance (INH and CAH). In the main these laboratory findings are unfavourable.

The relative value of CAH in early tuberculosis has yet to be determined, for its assessment to date has been with the chronic, and in many cases otherwise untreatable, forms of the disease.

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CENTRAL NERVOUS SYSTEM COMPLICATIONS DURING I.N.H. TREATMENT OF PULMONARY TUBERCULOSIS

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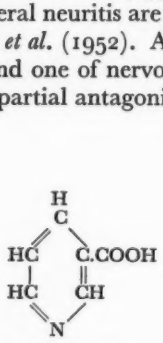
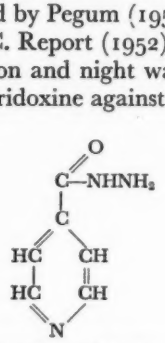
The mechanism of interference of action of a drug by a structurally related analogue may explain why patients treated with iso-nicotinic acid hydrazide (I.N.H.) may develop manifestations of nicotinic acid deficiency.

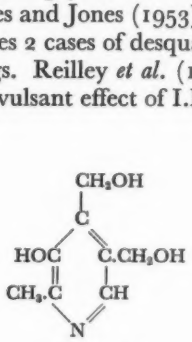
McConnel and Cheetham (1952) and Jones and Jones (1953) each describe a case of pellagra occurring during the course of I.N.H. therapy. Hunter (1952) and Zabad (1953) each describe a case of confusional psychosis. Cases of peripheral neuritis are described by Pegum (1952), Jones and Jones (1953) and Linton *et al.* (1952). An M.R.C. Report (1952) describes 2 cases of desquamation, and one of nervous reaction and night wanderings. Reilley *et al.* (1953) report partial antagonism of pyridoxine against the convulsant effect of I.N.H.



Nicotinic acid



Iso-nicotinic acid hydrazide



Pyridoxine

In this hospital 4 cases of confusional psychosis have developed during the course of I.N.H. therapy. Two cases who had psychoses of undiagnosed nature and were receiving I.N.H. were given nicotinic acid. One showed no change. In the other, Case 5, I.N.H. may have been a factor. Thirteen cases who were admitted with pellagra and subsequently received I.N.H. are described, and 2 with peripheral neuritis. All 20 cases are Bantu patients with pulmonary tuberculosis. Those who remained in hospital were followed-up until the middle of October 1953. Except where otherwise stated, the daily dosage of I.N.H. was 400 mgm. and of yeast 30 gr.*

Case Reports

Case 1.—M.Z., a female aged 30, was admitted in February 1951 and received P.A.S. and streptomycin.

On September 10, 1952, I.N.H. (8 mgm./Kg.) was added. On October 1,

* When I.N.H. first became available we decided to use 8-10 mgm. per Kg. of body weight, which was reported as the maximum safe dose.

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1952, at night, she was excitable, roaming round and praying loudly. In the morning she seemed normal. The next night a similar episode occurred. She said she was about to die. The following morning she apologised for having been a nuisance. That day, October 3, 1952, I.N.H. was stopped. On October 6, 1952, she was as before—quiet by day and noisy at night—but was no longer fully orientated during the day. The next day she had persecutory delusions and hallucinations. The C.S.F. showed no cells and normal chemistry.

The patient received phenobarbitone, chloral, and later bromides, but deteriorated mentally. As she was becoming unmanageable, electrical convulsive therapy was commenced. After two treatments on November 16 and 18, 1952, she was temporarily more tractable. However, she lost weight steadily and it became a struggle to make her eat. She would not obey the staff, was dirty in her habits and destructive. She wandered round unless sedated, resented interference, and once attempted to hit a nurse. She received the ninth and last of the series of E.C.T. on December 17, 1952.

From December 31, 1952, nicotinic acid 100 mgm. intravenously daily was given. There was remarkable day-to-day improvement. After three days she required no sedatives. After a week she was rational, ate better, and was no longer destructive. After two weeks she was more co-operative, no longer wandered round, but still required persuasion to eat. For the first time for some weeks other patients talked to her. She herself felt better, but would not discuss her recent illness. After three weeks she was clean in her habits, appeared well orientated in most respects, but at least one delusion was still present. One month after commencing treatment with nicotinic acid she was quite normal and had no delusions. She laughed at the delusions she was told about, but would not discuss them. Her memory for past events returned. She was well orientated, eating well and gaining weight. On January 28 1953, intravenous nicotinic acid was stopped and 400 mgm. daily was given orally.

On March 26, 1953, nicotinic acid was stopped and I.N.H. (8 mgm./Kg.) recommenced. No untoward symptoms developed.

Case 2.—N.X., a female aged 16, was admitted on October 14, 1952, with tuberculous meningitis, in very poor general condition, but intelligent and mentally alert. She received streptomycin, P.A.S. and I.N.H. 500 mgm. daily (12 mgm./Kg.). On November 17, 1952, she had periods of confusion. She was restless, shouted and bit her hands. In the intervals she appeared normal and did not know what had happened. The next day similar episodes occurred and I.N.H. was stopped. There were no further mental symptoms and on November 12, 1952, I.N.H. 400 mgm. daily (10 mgm./Kg.) was recommenced. Although there was no relapse, a course of nicotinic acid was given in January 1953.

Case 3.—S.C., a male aged 21, was admitted on August 8, 1952, in fairly good general condition. From August 13, 1952, he received I.N.H. (7 mgm./Kg.). On September 27, 1952, he suddenly developed a mania for religious preaching. He was restless, noisy, manneristic in speech and behaviour, and exhibited flight of ideas. Despite sedation, and insulin 30 units before breakfast daily, the mania increased. I.N.H. was discontinued. Relatives knew of no similar previous episodes. On October 3, 1952, he was transferred to a mental institution. When seen on his return in March 1953 and again in August 1953, mentally he appeared normal.

CASE 4.—F.H., a female aged 38, was admitted on December 15, 1952, in fair general condition, with a queer history of sudden onset, on November 7, 1952, of pain in the right arm, chest and leg and right unilateral headache. She received P.A.S. and I.N.H. (8 mgm./Kg.) for one month before admission and this was continued here. She improved radiologically and clinically until April, 1953. Domestic troubles may account, partly, for her subsequent deterioration.

From June 5, 1953, she complained with increasing frequency of headache, pain in the right side and tiredness. She appeared dull. On June 8, 1953, she had an attack reported as hysteria. The next day examination revealed hyperreflexia but nothing else of note. Thereafter anorexia and insomnia became progressively worse. For the headache and other pains the patient received about 30 gr. of aspirin daily combined with phenacetin, codein, etc.

On June 15, 1953, I.N.H. was stopped and nicotinic acid 400 mgm. orally daily commenced. The next night an episode of confusion occurred. The patient was noisy and had delusions. On June 17, 1953, for the first time for twelve days, she required no sedatives or analgesics. Thereafter she improved steadily. On July 7, 1953, nicotinic acid was reduced to 100 mgm. daily.

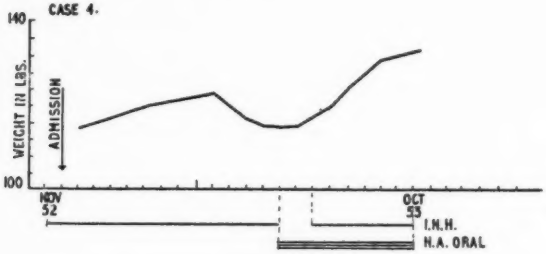

FIG. 1.

On July 14, 1953, I.N.H. was recommenced. On July 22, 1953, nicotinic acid was reduced to 50 mgm. daily. She was discharged in October 1953 to continue treatment at home (Fig. 1).

CASE 5.—V.K., a female aged 17, was admitted on August 28, 1952, in poor general condition, with calf tenderness and ankle clonus (not sustained). From September 3, 1952, she received streptomycin, P.A.S. and I.N.H. (10 mgm./Kg.). On September 22, 1952, she had an attack described as hysteria, and two days later another attack of shouting and incoherence. The C.S.F. showed no cells and normal chemistry. She was noisy and irrational during the next week. By October 1, 1952, she had reached a state of negation. On October 14, 1952, the C.S.F. was again normal. On October 16, 1952, I.N.H. was discontinued for one week. In November she was less apathetic but still had episodes of noisy, uncontrollable behaviour.. She insisted on going home. By December she was rational, and quiet on the whole, but was moody and offered violence to anyone who intefered with her. This position obtained for some months.

From July 22, 1953, she received nicotinic acid 100 mgm. intravenously daily for two weeks, followed by 300 mgm. orally daily. By October 1953 she has shown considerable improvement. Her appetite is good. She is well

orientated. She still keeps to herself, but tolerates teasing without retaliation (Fig. 2).

CASE 6.—F.K., a male aged 29, was admitted on May 13, 1952, with tuberculosis and leprosy, pellagrous dermatitis, and an indolent ulcer on the leg. From May 30, 1952, he received I.N.H. 200 mgm. daily (5 mgm./Kg.), yeast and nicotinic acid 300 mgm. orally daily. Two months later the ulcer was healing but dermatitis was still present, and I.N.H. was increased to 400 mgm. daily (9 mgm./Kg.). By August the pellagra had cleared. Supplements were discontinued in November 1952. He was discharged in December 1952 on disciplinary grounds.

CASE 7.—I.Z., a female aged 40, was admitted on May 20, 1952, in poor general condition, with pressure sores and pellagrous dermatitis and dementia. She received B Complex* 4 c.c. intramuscularly daily for five days, yeast, and from May 23, 1952, I.N.H. 200 mgm. daily (5 mgm./ Kg.).

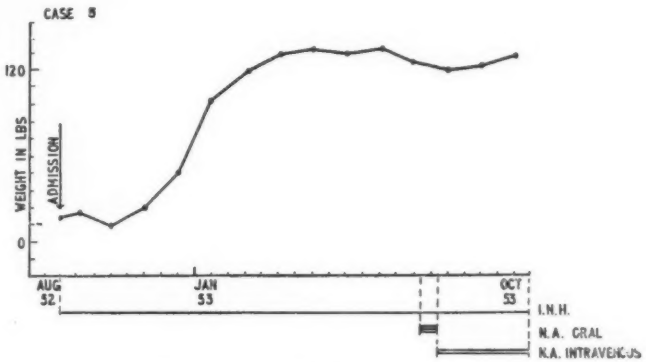

FIG. 2.

She improved greatly in the first two weeks. After a month she was still weak and confused, and incontinent of urine and fæces. She had glossitis and bilateral keratitis. I.N.H. was increased to 400 mgm. daily (9 mgm./Kg.). B complex 2 c.c. intramuscularly was given daily for one month. By July she was mentally normal. The pressure sores and dermatitis had virtually healed. In November 1952 she was very aggressive and was discharged on disciplinary grounds (Fig. 3).

CASE 8.—A.N., a male aged 15, was admitted on July 17, 1952, with pellagrous dermatitis and dementia, and calf tenderness. From July 25, 1952, he received I.N.H. (10 mgm./Kg.), yeast and nicotinic acid 300 mgm. orally daily. The pellagra cleared in October 1952. Supplements were discontinued in November 1952, He absconded in June 1953.

* 1 c.c. of the preparation used contains:

	mgm.
Thiamine hydrochlor.	10
Riboflavin	2
Niacinamide	100
Pyridoxine hydrochlor.	5
Ca Pantothenate	5

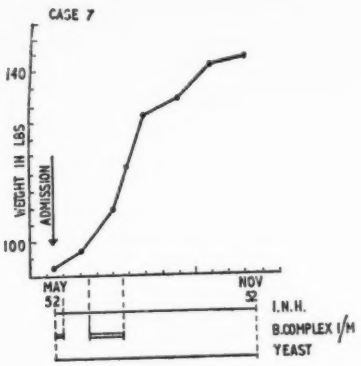

FIG. 3.

CASE 9.—Ed.M., a male, was admitted on July 29, 1952, with pellagrous dermatitis and glossitis. From August 1, 1952, he received streptomycin, P.A.S. and I.N.H. (10 mgm./Kg.) and yeast. Six weeks later the skin had improved, but roughness and pavementing of the legs and glossitis persisted. By January 1953 there was no further change and nicotinic acid 100 mgm. intravenously was given daily for one week. The skin improved. The patient was noticeably brighter, although his previous mental state had not been regarded as abnormal. In March 1953 glossitis was still present and nicotinic acid 100 mgm. intravenously was given daily for two weeks, after which the glossitis cleared (Fig. 4).

CASE 10.—M.C., a male aged 17, was admitted on February 6, 1953, with pellagrous dermatitis and a radiological diagnosis of tuberculosis. From February 11, 1953, he received streptomycin, P.A.S. and I.N.H. (8 mgm./Kg.). After two months he had deteriorated clinically and radiologically, and the diagnosis of tuberculosis was doubted as there had been no response to antibiotics and no bacteriological confirmation. Dermatitis was still present, and his tongue was slightly swollen and the edges were smooth. I.N.H. was stopped on April 23, 1953. The dermatitis of the arms cleared after three weeks and the glossitis after four weeks. After two months, although the legs had improved, the skin was still rough, and from June 20, 1953, he received B complex 1 c.c.

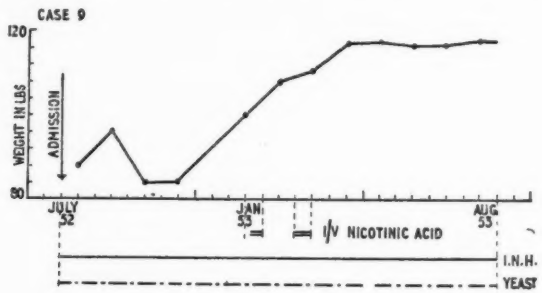

FIG. 4.

intramuscularly daily for one week. He improved markedly, and the pellagra cleared by July 10, 1953, when I.N.H. (7 mgm./Kg.) was recommenced. Bacteriological confirmation of tuberculosis was obtained later (Fig. 5).

CASE 11.—N.D., a female aged 45, was treated in another hospital for four weeks in September 1952 with streptomycin, P.A.S. and I.N.H., and left against advice. She was admitted here on November 14, 1952, with pellagrous dermatitis and dementia. The pellagra had cleared by November 26, 1952, when streptomycin, P.A.S. and I.N.H. (8 mgm./Kg.) was commenced.

CASE 12.—M.Ma., a male, received P.A.S. as an out-patient from October 1952. On March 11, 1953, I.N.H. was added. He was admitted on March 24, 1953, with erythema, pigmentation and commencing desquamation of hands and forearms, and glossitis. He said the rash appeared about a week before admission. P.A.S. and I.N.H. were continued, but from April 7, 1953, I.N.H. was withheld. The pellagra cleared by May 16, 1953, when I.N.H. (7 mgm./Kg.) was recommenced. In August 1953 the patient complained of burning feet. There was no other evidence of avitaminosis. From August 10, 1953, nicotinic acid 200 mgm. daily was given orally. After a week the

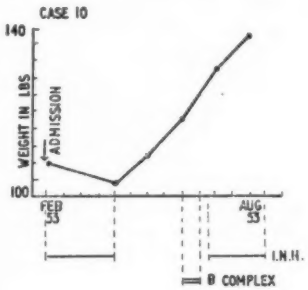

FIG. 5.

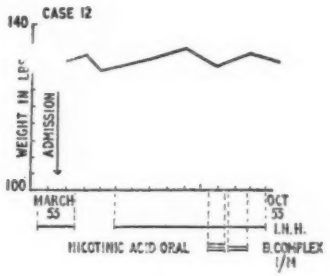

FIG. 6.

paræsthesias improved. A week later a course of intramuscular B complex was given. When discharged in October 1953 he still had mild paræsthesias. which were not incapacitating (Fig. 6).

CASE 13.—M.Md., a female aged 45, a chronic alcoholic and dagga smoker with two previous admissions, was seen as an out-patient on April 29, 1953, in very poor general condition. The skin of her legs and arms was dry and scaly. She was apathetic, but alcoholism made it difficult to assess her mental condition. She received P.A.S. and I.N.H., and was admitted one week later, mentally apparently normal. Two weeks after admission the skin appeared normal. She was discharged in October 1953 to continue treatment at home.

CASE 14.—C.Mz., a female aged 13, received P.A.S. and I.N.H. as an out-patient from June 5, 1953. She deteriorated and was admitted on July 28, 1953, with pellagrous dermatitis, glossitis and hyperreflexia. She received P.A.S., I.N.H. (14 mgm./Kg.), yeast and nicotinic acid 200 mgm. orally daily. By August 20, 1953, the glossitis cleared, but the dermatitis and hyperreflexia persisted. I.N.H. was stopped and B complex 2 c.c. intramuscularly was given

daily. By September 2, 1953, the skin appeared normal and I.N.H. was recommenced. Nicotinic acid was reduced to 50 mgm. daily on September 16, 1953.

Case 15.—V.V., a female aged 13, was seen as an out-patient on July 22, 1953, with marked malnutrition, and received P.A.S. and I.N.H. She was admitted on July 31, 1953, apathetic and disorientated for time, with pellagrous dermatitis, glossitis and vaginitis. There was wasting of the lower limb muscles, hyperreflexia and sustained knee and ankle clonus. She received streptomycin, P.A.S. and oral and intramuscular B complex, but I.N.H. was withheld. Two weeks later she was mentally normal, the dermatitis and clonus had disappeared, but hyperreflexia persisted. By August 19, 1953, the tongue appeared normal and the reflexes were less brisk. Nicotinic acid was reduced to 50 mgm. daily and I.N.H. (12 mgm./Kg.) was commenced.

Case 16.—M.S., a female aged 20, received P.A.S. and I.N.H. as an out-patient from July 16, 1953. She was admitted here on August 17, 1953, very ill and toxic, with a dry scaly skin, marked apathy, pain in the legs and extreme calf tenderness. From August 18, 1953, she received streptohydrazid 1 G. (equivalent to streptomycin 1 G. and I.N.H. 236 mgm.) intramuscularly daily for two weeks, then 1 G. every third day, yeast and nicotinic acid 200 mgm. orally daily. On August 24, 1953, she was more alert and the paræsthesias and calf tenderness had diminished. From August 27, 1953, she received B complex 1 c.c. intramuscularly daily for one week. On August 31, 1953, the paræsthesias were still present and a week's course of vitamin B_{12} was given with symptomatic improvement. She deteriorated clinically, was dull and unco-operative, and when pain in the feet returned towards the end of September nicotinic acid 300 mgm. orally and B complex 4 c.c. intramuscularly was given daily. In October 1953 she was brighter, no longer had paræsthesias, but had deteriorated radiologically and lost weight from 93 to 78 lb.

Case 17.—A.M., a female aged 40, was admitted on August 1, 1953, with pellagrous dermatitis, a smooth tongue and mild apathy. From August 5, 1953, she received streptohydrazid 1 G. on alternate days for fourteen days, then 1 G. every third day. On August 12, 1953, the dermatitis was unchanged, the tongue had become swollen, and nicotinic acid 200 mgm. orally was given daily. On August 19, 1953, the patient complained of painful feet, and the lips were dry and cracking. By August 24, 1953, the skin appeared normal and the glossitis and paræsthesias had improved. By September 3, 1953, there was no change and B complex 4 c.c. intramuscularly was given daily for one week. She had no further paræsthesias. By October 1953 the tongue and mental condition were normal.

Case 18.—C.Ma., a female aged 19, was admitted on August 11, 1953, with pellagrous dermatitis, glossitis and stomatitis. From August 12, 1953, she received streptohydrazid 1 G. on alternate days for fourteen days, then 1 G. every third day, yeast and nicotinic acid 200 mgm. orally daily. The pellagra cleared by August 31, 1953. On September 16, 1953, nicotinic acid was reduced to 50 mgm. daily.

Case 19.—Es.M., a female aged 36, was admitted on February 18, 1953, emaciated and toxic. She complained of burning feet and legs. No other

evidence of avitaminosis was found. She received streptomycin and I.N.H. (9 mgm./Kg.). On February 24, 1953, the edges of the tongue were smooth and the paræsthesias worse. Thiamine was given for one week without improvement. From March 1, 1953, nicotinic acid 100 mgm. was given intravenously daily for one week, after which the paræsthesias and glossitis disappeared.

CASE 20.— Et.M., a female aged 23, was admitted on May 5, 1953, in good general condition after two months' in-patient treatment at another hospital, followed by five months' out-patient treatment on P.A.S. and I.N.H. This was continued here and on July 22, 1953, the patient complained of itching feet, which she said she had noticed for some months. The skin of the toes was hyperkeratotic and the nails were thickened. No other signs of avitaminosis were found. She received nicotinic acid 200 mgm. orally daily. After one week the paræsthesias improved. After one month the paræsthesias disappeared, the skin appeared normal and nicotinic acid was reduced to 50 mgm. daily.

TABLE I.—THE COURSE OF THE 13 CASES OF PELLAGRA

	Case No.	*Time in which pellagra healed*	*Time from admission that I.N.H. was commenced*	*Whether supplements were given*	*Time in which pellagra healed after stopping I.N.H.*	*Remarks*
Group A	11	2 weeks	2 weeks after	No		I.N.H. not given until pellagra healed.
	13	2 „	1 week before	No		Did not have classical pellagra.
	15	3 „	3 weeks after	Yes		I.N.H. not given until pellagra healed.
	18	3 „	1 day after	Yes		Low I.N.H. dosage.
Group B	6	3 months	2 weeks after	Yes		Discharged for behaviour which may have been part of mild unrecognised pellagrous dementia.
	7	2 „	3 days „	Yes		
	8	3 „	1 week „	Yes		
	9	7 „	2 days „	Yes		Delay of 5 months in giving supplements.
	17	2 „	4 days „	Yes		Low I.N.H. dosage.
Group C	10	5 months	5 days after	Yes	3 months	Delay of 4 months in giving supplements.
	12	7 weeks	2 weeks before	No	5 weeks	Supplements given in relapse.
	14	2 months	2 months before	Yes	2 weeks	
Group D	16	—	1 month before	Yes		Low I.N.H. dosage. Did not have classical pellagra.

Discussion

The average case of pellagra will heal (at least as regards skin, mucous membrane and mental changes) in about two weeks on a good diet with or without supplements. The course of the 13 cases of pellagra is shown in Table 1. The 4 cases in group A conform to the average course. The 5 cases in group B healed in longer periods while I.N.H. was continued. The 3 cases in group C healed after I.N.H. was discontinued. The case in group D has not healed two months after admission.

TABLE II.—DEVELOPMENT OF SYMPTOMS ON I.N.H. THERAPY

Sign or Symptom	*In Hospital*		*At Home*	
	Developed	*Increased*	*Developed*	*Increased*
Dermatitis			?12	
Psychoses	1, 2, 3, 4	?5		
Peripheral neuritis	12, 17	19, 20	20	
Mucous membranc changes	19	17		
Deterioration of general nutritional state ..				14, 16

The confusional states may possibly be regarded as part of the pellagra syndrome, although only 1 case, 5, had other manifestations of avitaminosis B. The 5 cases had in common a state of confusion, with disorientation, loss of memory, delusions, hallucinations and mania in varying degrees. In cases 1, 2, 4 and 5, in the early stages the periods of confusion were episodic with intervening lucid intervals. Cases 1 and 2 had some insight. Cases 1 and 3 had a religious accentuation.

The development of symptoms on I.N.H. therapy is summarised in Table II. That exposure to sunlight is apparently essential for the development of pellagrous dermatitis, and that on admission patients are usually confined to bed may explain that no case of dermatitis has developed in this hospital.

Treatment

Pellagra.—It would appear that most cases of pellagra cannot be treated satisfactorily on a good diet, even with supplements, if I.N.H. is given concurrently. In fact, initial clinical deterioration occurred in Cases 9, 10 and 16. As regards the pulmonary condition, Case 16 probably belongs to that group of cases which deteriorate despite all treatment, but the subsequent course of Cases 9 and 10 places them outside this category. It is therefore suggested that if a patient has pellagra and tuberculosis, I.N.H. should be withheld until the pellagra is brought under control in two or three weeks.

Psychoses.—The response to treatment is summarised in Table III. Parenteral treatment in the early stages is suggested, but need not be prolonged, and would probably have avoided the attack of confusion in Case 4 the night after treatment was instituted.

Peripheral Neuritis.—The response to treatment is summarised in Table IV.

TABLE III.—RESPONSE TO TREATMENT OF THE PSYCHOSES

	Stopping I.N.H.	*Nicotinic acid*
Case 1	Nil	Dramatic
Case 2	Satisfactory	
Case 3	Unsatisfactory	
Case 4		Good
Case 5		Present
Hunter's Case	Unsatisfactory	
Zabad's Case		Good

TABLE IV.—RESPONSE TO TREATMENT OF PERIPHERAL NEURITIS

	Nicotinic acid	*Thiamine*	*Vitamin B_{12}*	*Vitamin B complex*
Case 12	Partial			Partial
Case 16			Temporary	Delayed
Case 17				Satisfactory
Case 19	Good	Nil		
Case 20	Good			
Jones and Jones, first case ..		Nil		
" " " second case	Satisfactory			
Some cases of Linton *et al.*				Nil. Dosage not stated

Conclusions

A relapse occurred in only 1 case in this series, Case 12 (excepting the aggressive behaviour of Cases 6 and 7), although in all except Case 3 I.N.H. therapy was either continued or recommenced. It is suggested that once a patient is " saturated " as it were with nicotinic acid he is less susceptible to the toxic effects of I.N.H. described here. It is suggested that once these effects have been exhibited, if I.N.H. is to be continued, a " maintenance " dose of nicotinic acid should be given. Beemer has shown that *in vitro* the sensitivity of the tubercle bacillus to I.N.H. is not impaired by adding to the medium nicotinic acid in one-eighth of the concentration of I.N.H. It would appear safe, therefore, to give 50 mgm. of nicotinic acid daily where 400 mgm. of I.N.H. is given daily. In this series the emphasis has been on nicotinic acid, but it is probably wise that other members of the B complex should also be used in curative and " maintenance " therapy.

I wish to thank Dr. B. A. Dormer, Medical Superintendent, for permission to publish this paper.

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PREDICTION OF MAXIMUM BREATHING CAPACITY FROM TIMED VITAL CAPACITY

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The Maximum Breathing Capacity (M.B.C.) test, sometimes known as the Maximum Voluntary Ventilation (M.V.V.) test, is now widely accepted as one of the more reliable indices of the ventilatory aspect of pulmonary function. The test procedure is, however, subject to certain objections.

1. It is exhausting for an ill patient, and possibly not free from the risk of spreading infection from diseased to healthy lung. Its use in patients with active tuberculosis is thus strictly limited.

2. The test requires full co-operation by the patient. In actual practice this is not such an obstacle as would at first sight appear likely, but sometimes enthusiasm tends to flag after a few seconds, and difficulty is inevitable when the patient has some reason for not wanting to appear quite physically fit.

3. Only an experienced observer can be sure when a maximal effort has been made.

An adequate alternative assessment of ventilatory ability cannot be obtained from the measurement of static volumes—*e.g.* Vital Capacity (V.C.)—for this takes no account of air flow speed; it is therefore necessary to measure the rate at which the V.C. can be used.

The Timed Vital Capacity (T.V.C.) has been shown by Gaensler (1951) in America, Kennedy (1953) in Great Britain, and Tiffeneau, Bousser and Drutel (1949) in France, to be a better indication of ventilatory function than is the Vital Capacity. The T.V.C. is that volume of the V.C. which can be delivered in a certain fixed time. Gaensler and Tiffeneau have each used a 1-second T.V.C., and Kennedy has used a 0·75-second T.V.C., but these very short time intervals require high-speed kymographs and other specialised apparatus; we have therefore investigated the possibility of estimating ventilatory capacity from the 2-second T.V.C., which can be measured on a standard recording spirometer.

From the T.V.C. we attempt to predict the result which would be obtained if the subjects were actually to carry out the M.B.C. test. This may be called the " predicted actual " M.B.C. and must be distinguished from the " predicted normal " M.B.C., the result which would be expected from a clinically normal subject. The latter prediction may be calculated from the subject's age, sex and body measurements (Needham, Rogan and McDonald, 1954).

The two values will be in agreement for normal subjects, but for others the " predicted actual " M.B.C. will generally be much lower than the " predicted normal " M.B.C.

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Method

The apparatus used will to some extent affect the speed with which the V.C. can be delivered, the important points being the weight of the bell and the cross-section diameter of the apparatus tubing. In order that comparable values of T.V.C. may be obtained the bell used should always be of the same standard type. It seems doubtful whether the very wide tubing and special mouthpiece apertures sometimes recommended for M.B.C. work are really necessary, for Gaensler (1951) has shown that a constriction in the apparatus tube has to narrow to about 15 mm. diameter before any reduction occurs in T.V.C. We have therefore considered the standard Palmer recording spirometer to be quite satisfactory, used with the valve removed, and with the faster of the two drum speeds. We have generally used the helium-dilution method lung-volume apparatus (Knipping modification) and so have had the advantage of air being circulated through the soda lime by the pump. When a machine without a pump is used it is better to remove the soda lime and valves, and switch the patient out of the circuit every 1½ minutes to allow the carbon dioxide to be rinsed out and more oxygen to be run in. Such carbon dioxide as does accumulate merely assists the procedure by making the subject breathe deeply.

The seated subject is asked to breathe quietly in the circuit for ½-1 minute, and then two trial measurements of V.C. are made (separated by a few quiet breaths). For these V.C. attempts stress is laid only on the volume to be produced. Next there are two measurements of T.V.C. (again separated by a sufficient number of quiet breaths to allow recovery), when the subject is urged in addition to exhale as quickly as possible. The emphasis on speed usually makes little difference to the performance, as there is a natural tendency to deliver the V.C. as fast as possible.

The method of measuring the 2-second portion of each V.C. is seen in Fig. 1. A Perspex set square is useful in reading the value, and could be calibrated to read off " predicted actual " M.B.C. The higher 2-second T.V.C. value is taken and if the 2-second T.V.C./V.C. ratio is to be calculated, then the greatest V.C. (not necessarily that belonging to the selected T.V.C.) is used. This is necessary as anxiety concerning speed sometimes reduces the total value.

The M.B.C. is determined using a standard Douglas double valve box and a 100-litre Douglas bag, the air in the bag being measured through a water-filled gasometer. The subject is instructed to breathe as deeply and as quickly as possible, and several preliminary trials are made. Finally, air is collected over a 15-second period, during which the subject is encouraged to maintain optimal rate and depth of breathing. A second attempt is allowed and the higher value taken as the M.B.C.

As it is unlikely that the large volume of air ventilated during an M.B.C. run will reach 37°C. fully saturated and the same objection holds to some extent with the T.V.C. determination, we decided not to adjust gas volumes to B.T.P.S. The temperature range observed during the work was 17°-22°C.

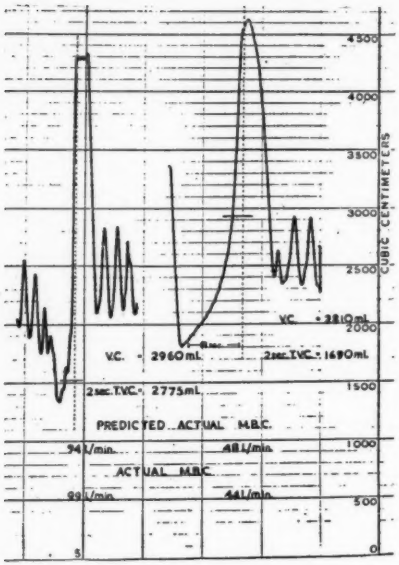

FIG. 1.—Spirogram showing measurement of T.V.C. in two men each aged 55 years. Normal on left. Emphysema on right. 1 vertical scale division=100 ml. 1 horizontal scale division=12 seconds.

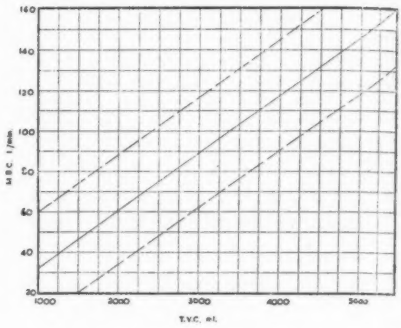

FIG. 2.—Regression of M.B.C. on T.V.C. for subjects under twenty years of age, including both sexes, and both normals and abnormals. The discontinuous lines on each side of the regression line represent approximately the 95% population limits.

MATERIAL

We wished to examine the relationship of the T.V.C. and M.B.C. not only in healthy subjects but also in patients suffering from a wide variety of conditions affecting the cardio-respiratory system, so that generally valid conclusions could be reached. Measurements of the T.V.C. and M.B.C. have been carried out on 623 subjects of both sexes, and of ages from 8 to 70 years. Table I summarises their clinical state, and Table II shows their age distribution.

RESULTS

The cases were divided into eight groups for analysis, according to whether they were male or female, over twenty years or under twenty years of age, and clinically normal or abnormal.

Mean values and standard deviations of age, height, weight, M.B.C. and T.V.C. for each of these groups are included in Table III.

A linear relationship was found to exist between M.B.C. and T.V.C. For the purpose of estimating the value of M.B.C. when T.V.C. is known, this relationship may be expressed as a regression equation linking the values. It was found possible to combine the four groups of cases under 20 years of age, but among the relationships for the other four groups there were small

TABLE I.—SUMMARY OF DISORDERS SUFFERED BY 305 CLINICALLY ABNORMAL SUBJECTS

Abnormality	*Nos. of cases suffering from abnormality*				
	Males (age ⩾ 20)	*Females (age ⩾ 20)*	*Males (age ⩽ 19)*	*Females (age ⩽ 19)*	*All groups*
Bronchitis	15	1	1	2	19
Bronchitis and emphysema	46	—	—	—	46
Emphysema and cor pulmonale	4	—	—	—	4
Asthma	10	7	4	—	21
Bronchiectasis	6	11	15	14	46
Carcinoma bronchus	26	4	—	—	30
Chest deformity	4	3	1	1	9
Heart { mitral stenosis	4	6	—	—	10
Heart { other	5	2	—	3	10
Sarcoidosis	1	3	1	—	5
Dermatomyositis	2	1	—	—	3
Hiatal hernia	1	6	—	—	7
Post-lobectomy	10	16	4	12	42
Miscellaneous { chest	33	6	1	—	40
Miscellaneous { other	9	3	1	—	13
TOTALS	176	69	28	32	305

TABLE II.—AGE DISTRIBUTIONS

Age (years at last birthday)	*Males*			*Females*			*Overall Totals*
	Normals	*Abnormals*	*Totals*	*Normals*	*Abnormals*	*Totals*	
Less than 11	—	2	2	—	9	9	11
11-13	29	11	40	24	4	28	68
14-16	24	10	34	24	9	33	67
17-19	25	5	30	24	10	34	64
20-29	27	10	37	18	20	38	75
30-39	23	16	39	13	21	34	73
40-49	22	49	71	11	10	21	92
50-59	20	62	82	16	11	27	109
60-69	10	32	42	8	4	12	54
70 and over	—	6	6	—	1	1	7
TOTAL	180	203	383	138	99	237	620*

* Ages of three adult abnormals not recorded.

but statistically significant differences. If these were ignored, a somewhat less reliable regression equation was obtained covering all the data. This is given, with the separate regressions, in Table III, but its use for predictions in individual cases is not recommended. The separate regressions are also shown graphically in Figs. 2, 3 and 4.

The overall regression is used, in Table IV, to obtain approximate "predicted actual" mean values of M.B.C. for each group, which are seen to agree well with the mean observed values. (Had the separate regressions been

TABLE III.—REGRESSIONS OF M.B.C. ON T.V.C. (WITH SUMMARY OF DATA USED)

Total No. of cases=623, split into eight groups, as follows:

A =Normal	Males, <20 years old.	B =Normal	Females, <20 years old.
A′=Abnormal		B′=Abnormal	
C =Normal	Males, ⩾20 years old.	D =Normal	Females, ⩾20 years old.
C′=Abnormal		D′=Abnormal	

Group		A	A′	B	B′	C	C′	D	D′	Total
No. of cases	.. ..	78	28	72	32	102	176	66	69	623
Age (years)	Mean	15·3	14·3	15·5	14·1	41·2	51·0	42·1	38·9	34·9
	S.D.	2·6	2·8	2·6	3·7	13·2	11·4	14·4	13·6	18·1
Height (inches)	Mean	63·2	60·5	61·9	58·7	67·8	66·9	63·0	62·9	64·4
	S.D.	5·7	5·3	4·1	5·6	2·5	2·8	2·3	2·4	4·5
Weight (lb.)	Mean	112·4	90·9	109·1	92·5	151·2	136·6	128·7	122·0	125·9
	S.D.	28·3	22·6	27·5	26·5	20·0	22·6	21·3	20·8	29·3
M.B.C. (l./min.)	Mean	102·4	70·6	88·9	56·7	121·3	65·2	83·6	59·0	82·8
	S.D.	31·4	29·7	20·9	20·7	23·8	29·5	16·4	20·7	33·6
T.V.C. (ml.)	Mean	3,440	2,530	2,870	1,880	4,000	2,250	2,670	1,980	2,770
	S.D.	980	940	620	620	830	850	560	690	1,060
Regression (*a*)			4·2			33·2	−2·3	24·9	15·5	3·7
Constants (*b*)			0·0285			0·022	0·030	0·022	0·022	0·0286
Standard error of (*b*)			±0·0010			±0·002	±0·001	±0·002	±0·002	±0·0006
Residual standard deviation			14			16	15	13	13	15
Correlation coefficient (M.B.C. and T.V.C.) ..			+0·89			+0·75	+0·86	+0·73	+0·73	+0·90

N.B.—Regression equations: (Predicted actual) M.B.C. (l./min.)=$a+b$ (T.V.C. in ml.).

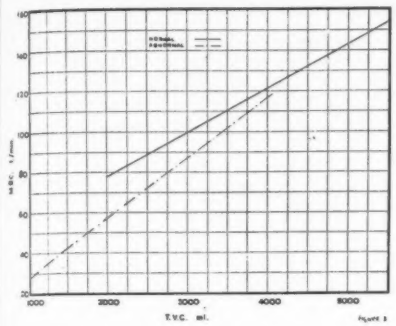

FIG. 3.—Regressions of M.B.C. on T.V.C. for male subjects over twenty years of age.

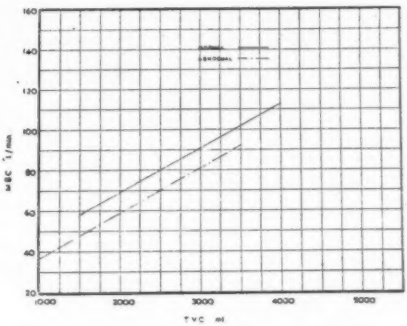

FIG. 4.—Regressions of M.B.C. on T.V.C. for female subjects over twenty years of age.

TABLE IV.—COMPARISON OF MEAN VALUES OF M.B.C. WITH PREDICTED "ACTUAL" AND PREDICTED "NORMAL" VALUES

Group	*No. of cases*	*Observed mean M.B.C.*	*"Predicted actual" M.B.C. (from regression on 2-second T.V.C. based on all 623 cases)*	*"Predicted normal" M.B.C. (from sex, age and body measurements)*
		Litres per minute	*Litres per minute*	*Litres per minute*
A	78	102·4	102·1	102·4*
A′	28	70·6	76·1	81·2
B	72	88·9	85·8	88·9*
B′	32	56·7	57·5	75·2
C	102	121·3	118·1	121·3*
C′	176	65·2	68·1	108·8
D	66	83·6	80·1	83·6*
D′	69	59·0	60·3	85·8
	623			

* In these cases the separate regressions are based on the observations quoted, and so the means necessarily agree exactly with the observed means.

used exact agreement would necessarily have been obtained because of the way the regressions are calculated.) On the other hand, the "predicted normal" values, calculated from the relationship of M.B.C. to age, sex and body measurements in normal individuals, are grossly in excess of the mean observed values in the abnormal groups.

A group of patients suffering from proven ankylosing spondylitis was found to have a mean M.B.C./T.V.C. ratio significantly higher than that for other abnormals or for normals. These cases were therefore excluded from this investigation, and the predictions given here should not be applied to them. This point will be discussed in more detail in a further communication.

Discussion

The 2-second T.V.C. prediction of M.B.C. appears to compare favourably with values obtained from 1-second T.V.C. by Gaensler (1951) and by Tiffeneau, Bousser and Drutel (1949). It is probably less accurate than the 0·75-second measurement reported by Kennedy (1953), but the 2-second has the advantage of requiring only standard apparatus.

The method is easy to carry out and only the exertion necessary for a V.C. is demanded of the patient. The M.B.C. predicted values are sufficiently close to the actual values to be of practical use, particularly in showing the smallest probable actual M.B.C. for a patient in whose case collapse or resection therapy is being considered.

The exact forms of the spirometric recordings are of interest, and Fig. 1 gives examples of these for a normal and an abnormal case. The slowing of expiration is obvious in abnormals, and it can be seen whether the slowing affects the whole length of the expiratory curve, as in emphysema, or only the terminal portion, as in narrowing of a main bronchus.

Note of Statistical Methods

Standard regression analysis technique was used in obtaining the prediction equations.

There were indications that the variability of results on each side of the predicted values tended to become greater with increasing T.V.C., and an attempt was made to eliminate this effect by applying some mathematical transformation to the results. This was abandoned when no clear advantage was found to accrue from the additional complication. The effect is not a large one and no serious consequences would appear to result from ignoring it, but it should be borne in mind in any further large-scale investigation of the relationship between M.B.C. and T.V.C.

Tests were also made to see whether the accuracy of prediction could be increased, within the separate groups studied, by taking account of variations in age, height, and weight, but it was found that no improvement was obtained over the regressions on T.V.C. alone.

Care should be exercised in comparing the correlation coefficients quoted in Table III, either with each other or with those obtained in other investigations. For example, the reason why they are smaller in the adult female groups than in the others is not because the relationship is less close in these groups, but simply because the range of variation of T.V.C. is less.

Summary

1. The 2-second T.V.C. and the M.B.C. have been measured in 623 male and female subjects aged 8-70 years, of whom 318 showed no evidence of cardiac or respiratory disease and 305 suffered from various disorders of these systems.

2. Equations have been calculated and graphs have been drawn to show the relationship between the M.B.C. and the 2-second T.V.C.

3. It is concluded that a useful prediction of the actual M.B.C. (as distinct from the predicted normal M.B.C.) can be obtained from the 2-second V.C.

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CHEMOTHERAPHY IN A CAIRO CHEST CLINIC

A Preliminary Report on the Methods adopted in Assessing the Value of Izoniazid, Streptomycin and Paraminosalicylic Acid in 122 Cases of Pulmonary Tuberculosis

By Attwa Ibrahim, Adib Boutros and J. B. McDougall*

Introduction

The treatment of pulmonary tuberculosis by the more recent compounds referred to in the sub-title above is a relatively new procedure in Government Chest Clinics in Cairo. In this communication an attempt is made to analyse the early results of such treatment in 122 patients selected as being likely to derive benefit from one or other, or some combination of the three preparations, Izoniazid (INAH), Streptomycin (SM) and Paraminosalicylic Acid (PAS). The guiding principle in the selection of patients was that the clinical range should be as wide as possible, since patients presenting themselves at this clinic display practically all the clinical varieties of tuberculous disease from early infiltrations to extensive bilateral cavitary manifestations.

The majority of patients live in an area where the environmental conditions are far from ideal. The Bab El Sharia Clinic covers a densely populated part of Cairo (200,000), not much more than two square miles in area. The population is predominantly Egyptian, though there are foci with strong admixtures of Greeks, Italians and other nationalities. The serious shortage of nursing staff at the clinic made it impossible for treatment to be given to more than a small number of patients in their homes, so that day-to-day supervision of patients was not possible. It is to be feared that this deficiency may continue for some considerable time, not only at the Bab El Sharia Chest Clinic, but in other Chest Clinics in Egypt, since financial limitations are likely to prevent any substantial increase in nursing personnel which should be available for home-visiting and treatment.

Nevertheless, it was felt desirable to ascertain how far chemotherapy might play some part in alleviating the problem for this mixed group of cases in the admittedly disadvantageous conditions under which the drugs had to be administered.

Yet another factor which prompted the introduction of chemotherapy was the serious shortage of institutional accommodation in the country. In the absence of adequate sanatorium and hospital facilities it has been found, as was to be expected, that, lacking prompt therapy, many patients deteriorated during the period of waiting for vacant beds, with a consequent development of progressive disease, leading to a clinical condition which precluded their

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admission to institutions. Some idea of the extent of this problem is obtained from figures given by Professor Sami of Cairo University; there are about four thousand beds for the treatment of tuberculosis in a population of over twenty million, in which it is estimated that the number of annual deaths from tuberculosis is in the region of 55,000. When this number of deaths is correlated with probable morbidity, the urgent need for active treatment outside institutions is emphasised, for it is certain that many years are bound to elapse before the number of beds will meet even minimum requirements of the tuberculosis population of this country. Any method, therefore, which may do something to overcome this impasse, even partially, deserves consideration and should be applied with diligence and enthusiasm.

The cases selected for this series had not previously received any form of treatment, with three exceptions which had had sanatorium treatment but had relapsed subsequent to their discharge from the institution.

At the very start, however, it was appreciated that there were two serious drawbacks: there were no opportunities for testing bacillary resistance in Cairo or for the culture examination of sputum. These defects have, of course, operated in previous studies in chemotherapy in Egypt, although the Central Laboratory in which bacillary resistance testing and culture examinations will be made is, at the time of writing, being equipped for these important functions. To what extent the absence of determinations in bacillary resistance and culture testing has militated against the accuracy of the present and previous work on this subject is impossible to say. Chemotherapy, in the absence of bacillary testing, is very much like " blind bombing "—a target may be reached, but precision can scarcely be expected for the physician is deprived of a valuable " radar."

Bacillary testing should, in fact, be made *before* chemotherapy is started in any patient, for there is little doubt that a number of patients harbour resistant bacilli prior to the first administration of any of the new drugs. The absence of culture examinations has been equally regrettable, for it is certain that the number of sputum-positive cases in this series falls considerably short of the actual number, since all examinations were limited to direct microscopy. The fact, however, remains that the conditions under which the present series of cases has been investigated are those which are likely to apply in many parts of Egypt, if not in Cairo, for some time to come.

Classification of Cases

The classification adopted has been that recommended by the Expert Committee on Tuberculosis of the World Health Organisation. This classification has been used in Denmark, in certain parts of New York State and elsewhere with satisfactory results. It was submitted for opinions to a number of countries in 1949 and 1950, and although there was favourable general comment, there was an almost universal desire to suggest modifications, or alterations in this code-system. Like all methods of classification, it is not one which is likely to gain general acceptance and, therefore, to become " standard." It has, however, the merit that it is based on objective findings only, for the sputum content and the radiological appearances alone for the criteria on

which the classification is based. There are of course certain lacunæ which will not satisfy the demands of the clinical pathologist. For example, the classification does not provide exact information as to the actual *extent* of a lesion. It will be seen that the X-ray appearances are described as belonging to one or both sides. If the lesion is confined to one side in which there is also the suspicion of a cavity, the lesion may be anything from a small area of apical infiltration to an extensive lesion involving the greater part of one side of the chest. It has, however, been this very difficulty in defining the extent of a lesion which has led to so many complications and differences of opinions in other classifications. The subjective interpretation of pulmonary pathology has been one of the greatest stumbling-blocks in most systems of classification. The margin of error in interpreting *objective* findings is, on the whole, much less, and when these are confirmed by two or more observers, they assume a value far beyond subjective impressions, however authoritative the observers may be.

" Radiological improvement " or " deterioration " has assumed an important role in assessing the results of chemotherapy in recent years, but it should be remembered that, although the X-ray film is an objective source of evidence, yet it is well known that its interpretation is subject to wide variations of opinion between different observers, and even by the same observer (Birkelo *et al.*, 1947).

Hilleboe has expressed the point well when he says: " The error in interpretation of X-ray films is of great moment in the epidemiology of tuberculosis, because the roentgenogram is the principal tool in diagnosis and follow-up of patients. If results are to be meaningful, the studies shou'd include provision for the interpretation of films by two or more well-trained observers." Further work in the United States of America (Yerushalmy, 1947) has shown that the real problem is not so much the quality or size of the film as the standardising of film-reading, and that it is just as important to have " standardised interpretation " as it is to have uniformity in purely technical processes.

It has perhaps been this variation in radiological interpretation which has led to some quite wide variations in results following chemotherapy in different series and in different countries. We would here refer to the extensive literature which has been collected by one of us (J. B. McD.) in connection with mass X-ray surveys (1949) and which shows that, in the diagnosis of non-clinically significant cases in particular, the variations in interpretation are frequently quite impressive. In chemotherapy studies a disturbing element is that almost every case treated shows some radiological evidence of pulmonary infiltration and/or evolutive disease, even when the predominant lesions are of a convincingly chronic type, with cavity formation and fibrous tissue prevailing over much of the pulmonary area. It is generally agreed that, from time to time, these sudden " flares-up " are extremely common in even the most advanced and apparently chronic cases, and it is no doubt these occasional advances in activity which keep out " chronic " cases—a constant menace both to themselves and others. In radiological interpretation, some would regard any slight clearing up of these evolutive changes as a sign of improvement, even if there is no corresponding improvement in the accompanying

chronic lesion in the chest. In the present series we have included under "radiological improvement" only cases which show evidence of change for the better in the main or predominant lesions, whatever their nature may be, and we have excluded from "radiological improvement" the slight changes which may have been noted in the more limited evolutive lesions so commonly seen in these chronic, advanced cases.

All films were read by two observers in the first instance, and a third observer read all the films independently without having any knowledge of the treatment prescribed, or the changes which may have resulted from the other objective methods used in this analysis.

The classification recommended by the Expert Committee on Tuberculosis of WHO, and adopted in this communication, is as follows:

Bacteriological findings:

1 Laryngeal swab NEGATIVE by culture.
2 Sputum NEGATIVE by culture.
3 Sputum NEGATIVE by direct microscopy (further examination not made).
4 Sputum not present; laryngeal swab not made.
5 Laryngeal swab POSITIVE by culture.
6 Sputum POSITIVE by culture.
7 Sputum POSITIVE by direct microscopy (+).
8 Sputum POSITIVE by direct microscopy (++).
9 Sputum POSITIVE by direct microscopy (+++).

NOTE: If the number of bacilli in the microscopic field averages 1-20, the result is recorded as (+); if the number per field is given as 21-100, it is recorded as (++); and if the number exceeds 100 per field the record is entered as (+++).

Reference may be made at this point to the work of Cruikshank (1952), who has given special attention to the estimation of the bacillary count in cases of tuberculosis both from the point of view of the patient and from the public-health standpoint. We are well aware that direct microscopy, using the Ziehl-Neelsen method, is a satisfactory procedure so long as there are many bacilli in the sputum. However, as Cruikshank points out, "Bacilli only become visible under enormous magnification, and, unfortunately, this entails equivalent enormous reduction in the field viewed. Even the cumulative field of a thorough scanning seldom covers more than 2 per cent. of the smear, and this means that there is a high probability that sparsely distributed bacilli will be missed altogether." Nevertheless, classification by visual procedure is widely used, and despite the tendency towards bias there is no question that gradings adopted by this method have statistical as well as clinical meaning. It is rightly asserted by Cruikshank that although a negative culture has several hundred times more sensitivity than a negative smear, yet both have meaning; the first is related to arrest of the disease, while the second is related to infectiousness.

It is clear that, by adopting this method of recording bacillary counts at successive stages of treatment, much valuable information may be obtained, and that the recording of "sputum plus," with degrees of "intensity" so to speak, assumes an important index in the assessment of progress.

X-ray findings:

0 No apparent lesion.
1 Lesion on one side only with no suspicion of cavity.
2 Lesion on both sides with no suspicion of cavity.
3 Lesion on one side only with suspicion of cavity.
4 Lesion on one side only with definite cavity.
5 Lesion on both sides with suspicion of cavity on one side.
6 Lesions on both sides with definite cavity on one side.
7 Lesions on both sides with suspicion of cavities on both sides.
8 Lesions on both sides, with definite cavity on one side, and suspicion of cavity on the other side.
9 Lesions on both sides with definite cavities on both sides.

Combining the Two Objective Factors in the Classification

As an example of the use of this classification, we may take a hypothetical case in which the sputum has been found negative by direct microscopy and where the X-ray film shows a unilateral lesion with suspicion of a cavity. This would be classified as 33, the first digit representing the bacillary findings, and the second digit the radiological findings. Again, if the sputum is positive by culture (digit 6), and the X-ray findings show that there is a bilateral lesion with definite cavities on both sides (digit 9), this case would be classified as 69.

It is obvious that the two digits 99 represent the most " serious " type of classification, since this signifies that numerous bacilli are to be found in each microscopic field, and that there is a bilateral lesion with definite cavities on both sides—a pathological state on which most would agree that the prognosis is most unfavourable.

It has already been mentioned that in this series we have been denied culture facilities for sputum examination, but in the performance of direct microscopy we have been greatly helped by Miss B. Eichkoff, who is a member of the international team now working at the Bab El Sharia Clinic, and who has had much experience in this technique in the State Serum Institute, Copenhagen. She has been responsible for the training of local staff in accordance with the standards applied to Copenhagen.

Grouping of Cases in the Present Series

Ideal as the above classification may be for the individual case, it is less convenient for grouping cases such as are to be found in a study of this kind. We have therefore condensed the above digit-code classification to more simple dimensions, and have considered three main groups as follows:

Group I : Lesions on one or both sides with no suspicion of cavity formation, whether the sputum is positive or negative.

Group II : Lesions on one or both sides with suspicion of cavity formation, whether the sputum is positive or negative.

Group III : Lesions on one or both sides with definite cavity formation, whether the sputum is positive or negative.

In one or other of these groups it is possible to include any given case. For example, the digit-code number 11 would represent a patient who has a negative result following laryngeal culture, together with a lesion on one side

with no suspicion of cavity formation (Group I); at the other extreme, the digit-code number 99 would represent, as stated above, a patient with numerous bacilli found by direct microscopy together with a bilateral lesion with demonstrable cavities on both sides (Group III). Between these two extremes lies a large number of possibilities any one of which can be indicated by the appropriate code number; in this way it is possible to follow the march of pathological events in any case.

Chemotherapy

Treatment was given either at the Clinic or in the homes of patients.

The drugs used in this trial were Izoniazid (rimifon, nydrazid, nidation and nicetal), Streptomycin and PAS. The doses used were very similar to those administered in many other trials. Izoniazid was given in doses of 300 mg. per day for patients of 60 kg. body weight, and adjustments were made in accordance with weight. Streptomycin was given intramuscularly twice a week in doses of 1 G., and here again adjustments were made to suit the weight of the patient; PAS was administered in 12 G. doses per day for five days per week, thus leaving a two-day interval every seven days. Where SM, PAS and Izoniazid were given, the Izoniazid therapy followed the treatment with SM and PAS; there were only two exceptions to this, when the three drugs were given simultaneously. It will be noted that in only two cases were SM and Izoniazid given together.

No patient was treated for less than twelve weeks and none for more than thirty weeks up to the time of reporting.

Commentary

Group I (cases with lesions on one or both sides with no suspicion of cavity formation).

Thirty-eight cases are included in this group. Only 10 had tubercle bacilli in the sputum by direct microscopy before treatment started. The diagnosis in the majority of cases in this group was therefore established by physical examination and radiological appearances in accordance with the methods described above. It is certain that, in this group in particular, bacilli would have been found in a much larger number of cases had we had access to culture examination.

It will be seen that there was evidence of radiological improvement in 30 cases (79 per cent.); it is obvious that the least severe types of disease were found in this group. Weight increase was recorded in 19 cases (50 per cent.), and the general condition was adjudged improved in 74 per cent. Seven of the original 10 open cases showed a reduction in the sputum bacillary count.

Group II (cases with lesions on one or both sides with suspicion of cavity or cavities).

There are 37 cases in this group, and 22 had tubercle bacilli in the sputum by direct smear before treatment started. In this group, 27 (73 per cent.) demonstrated some radiological improvement; about the same number, 26, showed an increase in weight, and the general condition was improved in

30 cases. The bacillary count was reduced during treatment in 13 cases out of the original 22 with bacilli in the sputum (59 per cent.). It should be noted that the sputum-positive cases in this group would almost certainly have shown an increase had culture tests been made.

Group III (cases with lesions on one or both sides with definite evidence of cavity formation).

This is the largest group and consists of 47 cases, all with very advanced lesions. Tubercle bacilli were found by direct smear in 31 cases at the start of treatment, and during treatment a reduction in the bacillary count was noted in 22. This group may well be considered a most severe test for any form of medication under the conditions prevailing in chest clinic practice. The preponderance of adult males is to be noted. Marked radiological improvement is not to be expected in cases of this type, but the fact remains that there was agreement between all observers that in 30 cases (63 per cent.) there was some evidence of reduction in the extent of the main lesion, sometimes with definite diminution in the size of cavities. It is our impression that many of the changes to be noted on the X-ray films of advanced cases following chemotherapy are due to the resolution of inflammatory changes in and around the existing fibro-caseous lesions, and more particularly in the bronchi leading into cavities, with consequent relief in intracavitary tension.

Equally interesting in this group is the fact that over 60 per cent. of cases showed an increase in weight and improvement in general condition. But perhaps the most significant finding is that among the 31 cases with bacilli in the sputum at the beginning of treatment, 22 (70 per cent.) showed a reduction in the bacillary content during the period of investigation. On the other hand, only 5 cases (16 per cent.) showed an increase in the bacillary count.

Discussion

If we take the combined groups and compare them with some other investigations of a similar nature, we find that radiological improvement was noted in 87 cases (71 per cent.), which is slightly higher than the combined results in the latest series published by the Medical Research Council (London, 1953), which was 64 per cent. This difference may well be due to the relatively shorter period during which our cases have been observed, for it is the general experience that sometimes marked changes take place during the period immediately following chemotherapy.

Weight increases were registered in 76 cases (62 per cent.), which is definitely lower than the London figure. In the M.R.C. it was reported that " all cases did well." The important factor operating here may be that in most investigations of this type the patients treated were simultaneously receiving sanatorium treatment, which of course was denied to the patients in this series.

The general condition of our patients was improved in 92 (75 per cent.), which compares with the range of 51 to 87 per cent. in the M.R.C. series, the variation depending upon the particular drug or combination of drugs used.

Diminution in bacillary content resulted in 42 cases (34 per cent.) in the

entire series, but comparisons cannot be made with other studies from this standpoint; at least, we have not had access to any records which have studied this particular feature. Conversion of sputum resulted in 26 cases out of a total of 63 with positive sputum at the beginning of the trial (40 per cent.). This is lower than the M.R.C. results, which showed sputum conversion in 55 per cent. (SM and PAS) at the end of three months; in 67 per cent. (SM and INH) at the end of three months, but in only 35 per cent. (INH alone) at the end of three months.

No symptoms of toxicity from any form of treatment came to our notice during the investigation.

In their comments on the administration of Streptomycin and PAS in a group of patients under their care, Sami and El Warraky (1953) made an observation confirmed by our limited experience in this present series; we agree that " the application of measures of collapse therapy has not been narrowed after the use of these specific drugs." We would confirm further that, " on the contrary, more patients have been rendered fit to undergo such treatment." In 9 cases in this series a successful pneumothorax was produced where, prior to the introduction of chemotherapy, any form of collapse therapy appeared to be out of the question.

It has not been the purpose of this investigation to attempt to assess the relative values of drugs used singly or in combination. Rather has it been our endeavour to evaluate the immediate results of chemotherapy in a typical out-patient tuberculous population. The present series will be kept separate from a second series which is now being collected, and in which treatment will be confined to the administration of INAH and PAS. This second series will to some extent provide a comparison with the present one, for the aim is to ascertain what may be the most satisfactory method of chemotherapy for chest clinics to undertake under the conditions prevailing in Cairo, always bearing in mind the large number of patients likely to be in need of such treatment, the shortage of institutional accommodation, and the relatively small numbers of nursing staff available for administering domiciliary treatment.

If the results of other chemotherapeutic trials are any guide, it would appear inevitable that such improvement as has been recorded in a number of patients in this initial series will fail to be maintained. The results may be ephemeral and unrewarding, especially in the groups which have received INAH alone. In this communication we have presented factual evidence only on the immediate results of chemotherapy in a chest clinic without recourse to the benefits of institutional treatment, and we are satisfied to leave the final assessment to the time when the cases have been followed up over a longer period of time.

ADDENDUM

A Follow-up of 71 Cases included in the above Study

For six months following the conclusion of the above study, an attempt was made to follow up as many cases as possible. Since many of the patients,

especially in Group III, were in an advanced stage of the disease, it was expected that a more definite picture of the effects of chemotherapy would be obtained with the passing of this extra time.

Reference was made in the main report to the shortage of nursing staff, and this defect was only too apparent when the vital question of follow-up of patients was considered, for it was found that, out of a total of 122 cases in the preliminary study, only 71 could be traced (58 per cent.), despite the small area covered by the Bab El Sharia Chest Clinic. Though we endeavoured to check on the exact addresses of patients when the trial started, we soon discovered that many had given false addresses, and were found not to be domiciled in the area at all. These patients had been prompted to attend the clinic in 1953 because of the special treatment facilities which they knew existed, and which were not at that time available at any other clinics in the city. Other patients were found to have accumulated supplies of drugs given to them at the clinic, because they felt that " they were so well that they did not think further treatment necessary." Some frankly refused to return to the clinic since they had, in their own opinions, recovered sufficiently to warrant a return to work, and did not want to have any further contact with a tuberculosis clinic. These points are of interest, since they emphasise the need for a very thorough home-visiting service in an area and population of the type with which we have to deal in the centre of Cairo, where modern chest clinic methods are comparatively new, and where so many patients still regard " recovery " from tuberculosis as synonymous with temporary amelioration of symptoms. A well-developed home-visiting service is necessary, not only to ensure the continuation of treatment, but to follow-up each patient with a view to determining the real efficacy of the drugs supplied.

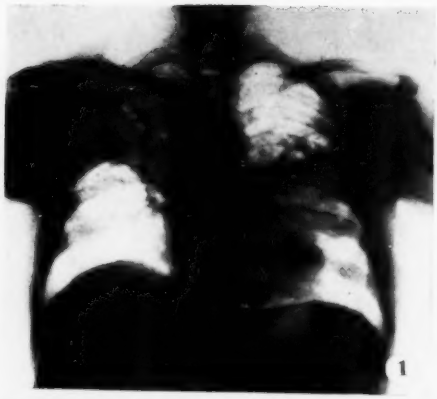
Of the 71 cases it was possible to trace with certainty, the period of observation has, therefore, been from nine to thirteen months, but even with this number there was a period of some six weeks during which there was an interruption of treatment owing to a deficiency in the supply of drugs. It is obvious that a clinical trial of this kind cannot be expected to produce satisfactory results if there are interruptions of this nature in the supply line. Though we have no direct evidence on the point, it is probable that a certain number of patients in the original group of 122 did not return to the clinic because of this failure on our part to continue treatment in a regular and sustained manner. Fortunately, the supply difficulties have now been overcome so far as this clinic is concerned, and treatment of patients is proceeding with regularity.

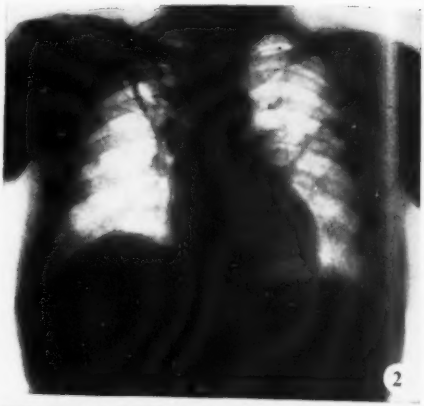
Of the 71 cases which have been under observation for the period of nine to thirteen months, the following is the classification, based on that used in the preliminary study (see above).

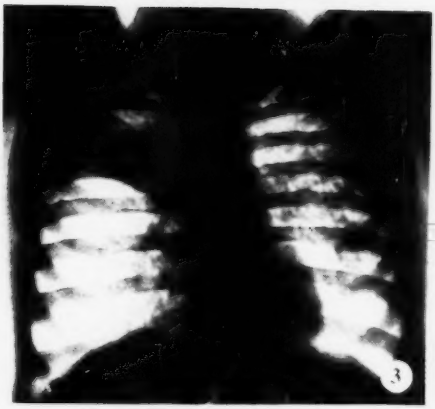
Group I (cases with lesion on one or both sides with no suspicion of cavity formation).

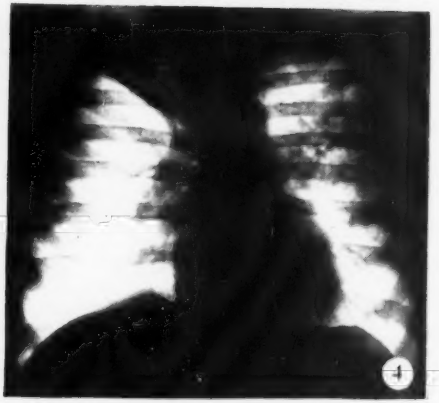
Twenty-two cases are in this group, 15 males and 7 females. Only one patient received some form of treatment (artificial pneumothorax) other than chemotherapy. Radiological improvement has been maintained in 19; in the remaining 3 the appearances are stationary.

PLATE I









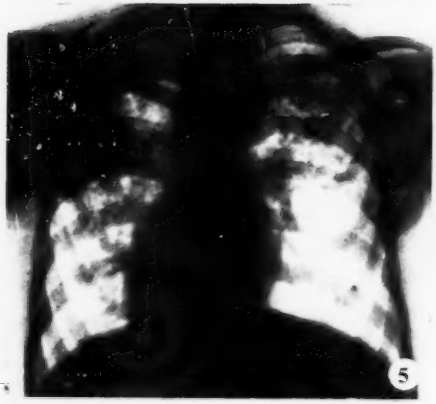


FIG. 1.—Serial No. 1700. Age 60. 4.4.53. Right upper zone and left mid. zone show fibro-caseous lesions with breaking down. Sputum +++. A diabetic subject. 43 g. S.M., 1,080 gm. PAS.

FIG. 2.—26.9.53. Exudative lesions both sides largely resolved, leaving strandy opacities with residual cavities right upper zone. Sputum neg. direct smear three consecutive times. Weight increase 4·5 kg. Cough and expectoration markedly diminished. General condition fair.

FIG. 3.—Serial No. 884. Age 23. 15.3.53. Fibrocaseous lesion right upper lobe with large cavity: inter-lobar septum raised and thickened. Left mid. zone shows infiltration. Sputum +++. 30 g. S.M., 720 g. PAS, followed by 20,000 mg. INH.

FIG. 4.—27.9.53. Marked resolution exudative elements especially right side: large cavity now obscure. Sputum neg. Weight increase 5 kg. Cough and expectoration much diminished. General condition fair.

FIG. 5.—Serial No. 2348. Age 18. 23.4.53. Extensive bilateral upper and mid. zone fibro-caseous disease with infiltration. Sputum pos. 45 g. SM, 1,080 g. PAS.

FIG. 6.—5.10.53. Significant reduction and resolution of original lesions on both sides. Sputum neg. after three consecutive smear examinations. Weight increase 11 kg. Cough and sputum much diminished. General condition remains fair.

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In the patients who were negative at the outset of the trial, the sputum has remained negative to direct smear: in 6 in which the sputum was originally positive it became and has remained negative in 2; the bacillary count has fallen progressively in 4 cases.

Weight increase has been noted in 18, and the general condition is stated to be improved in all but 1. This group of cases is, of course, the most favourable from the clinical standpoint.

Group II (cases with lesion on one or both sides with suspicion of cavity or cavities).

There are also 22 cases in this group, 15 males and 7 females, which happens to be identical with Group 1. No patients in this group received any treatment other than chemotherapy during the period of observation.

Radiological improvement is reported in 17; 1 case is worse, and in 4 the X-ray findings are reported as stationary.

None of the cases originally negative have so far become positive by direct smear examination, and of the original 9 positive cases, 5 have shown a reduction in the bacillary count.

In 1 case only there has been a loss of weight, and in 3 the weight has remained stationary; all the others have shown an increase in weight.

The general condition is regarded as having improved in all but 3 cases.

Group III (cases with lesions on one or both sides with definite evidence of cavity formation).

There are 27 cases in the group, 19 males and 8 females. In 4 patients artificial pneumothorax was induced during the period of observation.

Radiological improvement is noted in 22 cases[1]; in 2 there has been definite retrogression and in 3 no change can be detected.

Of the 16 patients in whom the sputum was positive at the beginning of treatment, only 1 has become negative. Twelve have shown a reduction in the bacillary count, and in 3 cases the count has remained stationary or has deteriorated.

Twenty-one out of the 27 cases have shown an increase in their original weight; only 1 has lost weight and the remaining 5 have remained stationary.

The general condition has improved in 17.

Taking the three groups together, the combined results are as follows:

Total cases	71
Radiological improvement	58 (81 per cent.)
Sputum conversion from positive to negative	4 (13 per cent.)
Sputum bacillary count reduced	21 (70 per cent.)
Weight increase	57 (80 per cent.)
General condition improved	53 (74 per cent.)

Comments

The cases represented in this Addendum may be regarded in some ways as being a selected group in so far as they probably constitute the most co-

[1] The criteria for assessing radiological improvement are given in the preliminary section of this report.

operative of our patients, and there is good reason to suppose that, had the sample been increased by the inclusion of a larger number of patients from the original Group III (which contained 47 relatively advanced cases), the results would have been less favourable.

However much the radiological and laboratory findings may fall short of the ideal, and however inferior the general results may be in comparison with those obtained with chemotherapy under strict sanatorium conditions, there seems to be little doubt that they are an advance on pre-chemotherapeutic days when most patients were allowed to remain untreated in any way other than by an occasional artificial pneumothorax operation, or by simple medication for the relief of outstanding symptoms. It has indeed been the benefits accruing from chemotherapy that have led chest clinic medical officers to resort more and more to chemotherapy, especially in the many countries where mortality and morbidity incidence is still far above the levels now being reached in the Scandinavian and North American countries.

In this series an impressive finding has been the increase in wieght and improvement in general condition recorded in so many patients, quite apart from the radiological and laboratory interpretations. Even allowing for the fact that the assessment of an " improved general condition " is not capable of the same precise analysis from the purely objective standpoint as laboratory findings or even radiological features, yet one cannot help feeling that the claims of other workers that some, at least, of the new chemotherapeutical agents exert specific metabolic effects, quite apart from their bacteriostatic and perhaps even bactericidal powers, may be justified. It may, of course, have been that the instructions given to our patients on the need for rest during treatment may have contributed in some degree to the amelioration in their general health. It has been one of the outstanding impressions in this trial that many patients have declared themselves to be " fit and well " in the presence of only slight radiological improvement, and even when there has been no alteration in the bacteriology of the sputum. This may raise the question of the virulence of bacilli following courses in chemotherapy, and one must await further research on this matter before any dogmatic statement can be made.

There can be no substitute for well-planned domiciliary care and the careful personal supervision of every patient, for in this way we can obtain not only the best results from chemotherapy, but also from the training and education of the patient and his family in the fundamental aspects of tuberculosis control. It may even be that the emphasis given to chemotherapy might, if overdone, detract from the paramount part which prevention has to play in the reduction of the entire problem of tuberculosis as an endemic disease. For this reason we prefer to regard chemotherapy as a part, and only as a part, of the campaign against the spread of the disease; however valuable the new drugs may be, and whatever clinical effects they may produce in individual patients, the sheet-anchor in control will always be in the effectiveness of the chest clinic services and the role they may take in case-finding, accurate diagnosis, prevention and close supervision of the patient and his family in the home.

Summary

The results of chemotherapy in a group of 122 patients attending a chest clinic in the city of Cairo are presented. The reasons for advocating this innovation into dispensary practice in Egypt are given, and special reference is made to the extremely limited institutional accommodation in the country.

During this trial no sensitivity testing or sputum culture facilities were possible, though this defect has since been remedied by co-operation between the Egyptian Government and WHO.

The classification used for patients under treatment is that recommended by the Expert Committee to the World Health Organisation, but which has not been widely adopted. It conforms to a modified code-system in which objective evidence of radiological signs and sputum examination are the two most important features.

The cases are divided into three groups: (*a*) Cases with lesions on one or both sides of the chest with no suspicion of cavity formation; (*b*) cases with lesions on one or both sides of the chest with suspicion of cavity formation; and (*c*) cases with lesions on one or both sides of the chest with definite evidence of cavity formation.

In the combined groups, radiological improvement was noted in 87 cases (71 per cent.); weight increase in 76 cases (62 per cent.); the general condition improved in 92 (75 per cent.), and diminution in the bacillary count resulted in 42 cases (34 per cent.). Conversion of sputum was noted in 26 cases out of a total of 63 with positive sputa at the beginning of the trial (40 per cent.). No symptoms of toxicity were observed during the trial.

A follow-up of 71 cases included in the first part of the study was made, and the difficulties associated with such a follow-up are described. The complete period of observation of these cases was from nine to thirteen months. Radiological improvement continued in 81 per cent., sputum conversion was maintained in 13 per cent., the bacillary count was reduced in 70 per cent., and weight increase and improvement in the general condition ranged from 70 to 80 per cent.

It is concluded that, however much the findings may fall short of the ideal, there seems little doubt that they are in advance of what appertained in this country prior to the advent of chemotherapy. Good home-visiting services and supervision during the period of treatment are even more necessary in Cairo than in many other large centres of population. Chemotherapy must always be associated with an effective chest clinic practice, and never be regarded as a substitute for essential measures in tuberculosis control.

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FOREIGN BODIES IMPACTED IN THE ŒSOPHAGUS

A RECORD OF SOME UNUSUAL CASES

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The Impacted Foreign Body

The swallowed foreign body which impacts in the œsophagus does not give rise to the same dramatic episode as an impaction in the air passages (Asherson, 1953). Nevertheless, it is liable to prove fatal, as is shown by the records of coroners' courts reported in the daily press. Such fatalities may result directly from the infective complications of impaction in the œsophagus (mediastinitis). Only too frequently, however, the cause of the death is the anæsthetic or a complication of the endoscopic instrumentation undertaken for its removal. This may result in a perforation of the œsophagus or mediastinitis.

A swallowed foreign body often impacts in the œsophagus just below the crico-pharyngeal sphincter, at the level of the thoracic inlet. It may be a spiked bone from a fish, a chicken or a rabbit; or a flat bone with jagged edges, such as a portion of a chop bone; or a circular metallic body, such as a coin, halfpenny, penny or threepenny piece (twelve-sided) or the lid of a pepper pot (Case 4); it may even be a large soft bolus of partially masticated meat (Cases 6 and 7).

The foreign body may remain impacted until dislodged by manipulation or removed through the œsophagoscope. After being impacted for some time it may become dislodged spontaneously. Accordingly, when the patient has travelled from another hospital where the impaction has been located radiologically, the X-ray should be repeated before œsophagoscopy, as this may have occurred and the foreign body may have passed lower down into the stomach. In a case in my experience it was dislodged by vomiting.

On the other hand, the foreign body may impact in such a way that the point penetrates the wall of the pharyngo-œsophagus. The entire foreign body may even be forced through a tear in the posterior wall to embed itself in the pre-vertebral tissues, the rent healing over. It may remain *in situ* for months, almost symptomless (Case 4).

The point of the foreign body alone may abrade or perforate the œsophagus. Surgical emphysema, a retro-œsophageal abscess (Case 5) or a mediastinitis may develop, even after the foreign body has been removed or spontaneously dislodged.

Any of these complications may require treatment, although the real cause (*e.g.*, the impacted foreign body) may be overlooked.

A spiked or pointed swallowed foreign body, such as an open safety-pin, may impact in the mid-œsophagus (Asherson, 1952). After some time it per-

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forates or ulcerates into the aorta or other great vessels, resulting in fatal hæmorrhage. Its presence may be unsuspected, as in the pre-radiographic days. Many museum specimens exist showing such a fatal outcome.

On the other hand, it may pass into the stomach and impact or perforate at any point in the intestinal tract—*e.g.*, in the cæcum or in the rectum. Elongated bodies such as a pencil may be unable to negotiate the pylorus.

A foreign body, pointed or not, may pass through the food passages uneventfully.

The inadvertently swallowed and consequently unsuspected foreign body manifests its presence in two ways:

1. By impacting within the cervical or thoracic œsophagus.
2. By perforating the posterior pharyngo-œsophageal wall to embed in the pre-vertebral region.

Normally, but not invariably, impaction gives rise to sudden and immediate symptoms. The patient may be unaware of having swallowed the foreign body, which becomes impacted and gives rise to a dysphagia, gradual in onset, mild in intensity, but sooner or later sufficiently intense to cause him to seek advice (Case 4). The patient, regardless of his age, for some time may remain unaware of the original incident. The case may thus run an anomalous course, particularly in institutions for mental defectives or among mental hospital patients.

Cases of Dysphagia due to Impaction of Foreign Body without any History of it

Case 1.—*Dysphagia in a child, due to a fish bone impacted in the œsophagus.*

A child, aged 2 years, was observed for over a year to swallow solids with difficulty. Swallowing occasionally precipitated a bout of coughing. The dysphagia was intermittent, and alike for fluids and solids. There was no history of swallowing a foreign body. Physical signs were absent.

The child was well nourished and had not lost weight (1 stone 8 lb.). There was an obvious dislike for taking food, but no pain on swallowing. The X-ray (see Fig. 1) showed a hold-up of the opaque meal just below the cricopharyngeus, with a widening of the retro-œsophageal space. The trachea was compressed. The condition was suggestive of a neoplasm.

The radiologist's report (Dr. C. J. Hodson) read: "There is a swelling in the thoracic inlet, displacing the trachea forward and compressing it markedly. The barium in the œsophagus tends to stick at this level (see Fig. 1). The appearances suggest an œsophageal neoplasm, a screen examination is advisable. There is no evidence of right-sided aorta or other vascular abnormality."

Œsophagoscopy revealed a long and flat gelatinous fish bone, impacted longitudinally in the long axis of the œsophagus. It was removed and swallowing was restored to normal.

Case 2.—By contrast, in the following case, an infant of 18 months was eating fish when the mother noticed that he coughed and spat out blood. No dysphagia developed subsequently.

The X-ray (Fig. 2) shows the vertebra of a fish impacted at the level of the fifth and sixth cervical vertebræ, in the œsophagus. It was removed by œsophagoscopy. Recovery was uninterrupted.

CASE 3.—*Dysphagia due to tooth plate swallowed without the patient's knowledge and impacted in the œsophagus.*

In the following case, an elderly debilitated man aged 75 complained of difficulty in swallowing for a few days. He was in a nursing home, and had had a serious abdominal operation recently.

The X-ray (Fig. 3) revealed a large upper denture impacted in the œsophagus. The patient was not aware of having swallowed it.

It was easily removed by œsophagoscopy.

Dysphagia due to a foreign body embedded behind the œsophagus.

A man of 40 whilst eating an egg, gulped down the metallic lid of a pepper pot. The incident passed completely out of his mind. Three months later he complained of vague dysphagia. There were no physical signs. An X-ray revealed a metallic foreign body, apparently impacted in the œsophagus. Confronted with this, the man recollected the incident referred to.

It was assumed (erroneously, as was later shown) that the foreign body was impacted *within* the lumen of the pharyngo-œsophagus. Œsophagoscopy (repeated on three separate occasions by three surgeons) failed to locate it. It was assumed that it had passed into the stomach. Subsequent X-ray showed the foreign body still *in situ*.

A fourth endoscopy, some time later, detected a sinus leading to the retro-pharyngo-œsophageal region, where the foreign body was embedded.

After removal the dysphagia abated.

CASE 4.—*Dysphagia due to a metallic foreign body (lid of a pepper pot) perforating the retro-pharyngo-œsophageal space, remaining* in situ *and almost symptomless, for over three months. Removal. Recovery.*—This man, first examined by me in 1933 at the Central London (now the Royal National) Throat, Nose and Ear Hospital, was later under the care of Mr. H. Kisch, F.R.C.S., to whom I am indebted for use of this case record.

1933. A man aged 44 attended the out-patients' complaining of some slight difficulty in swallowing for the past three months. No other history was volunteered, nor could be elicited. The dysphagia was slight. He had not lost any weight. The only physical sign was a small collection of secretions visible on mirror pharyngoscopy in the hypo-pharynx.

Routine radiography disclosed a large circular perforated metallic foreign body, apparently impacted in the pharyngo-œsophageal region. On drawing the patient's attention to this, his wife recollected that the patient had swallowed the top of a pepper pot which had dropped into an egg, the wife adding apologetically that her husband was " no scholard." (Figs. 4 and 5.)

This case shows that even a large disc-shaped body which has become impacted may penetrate the wall of the swallowing passages and that the intruder may remain there for months with little or no symptoms or suppuration. The actual ingestion may be forgotten.

Endoscopy was negative. It was assumed that the foreign body had been dislodged into the stomach. Another radiograph, much to the amazement of the operator, showed the foreign body still *in situ*. A second endoscopy a week later, proved negative and another X-ray showed the foreign body in its original position. Subsequently, very careful searching of the posterior wall disclosed a small patch of granulations, beyond which the foreign body could

PLATE II

FIG. 1.—Fish bone impacted in the œsophagus of infant aged 2. Lateral view. Swelling in the thoracic inlet compresses the trachea and suggests an œsophageal neoplasm.

FIG. 2.—Fish bone impacted in the œsophagus of infant aged 18 months. X-ray shows bone at level of 5th and 6th cervical.

FIG. 3.—Tooth plate impacted in pharyngo-œsophagus.

FIG. 4.—Perforation of the œsophagus by the metallic lid of a pepper pot which became embedded in the retro-œsophagal space. Anterior-posterior view shows the lid at the level of the pharyngo-œsophagal junction. The air shadow of the trachea can be observed, tapering above towards the vocal cords, which are obscured by the radio-opaque foreign body. The foreign body is outside the lumen in the posterior visceral space. This can be determined by a lateral view, with an opaque swallow.

FIG. 5.—Lateral view. This shows the cap embedded in the pre-vertebral space which is considerably broadened (cf. retro-pharyngeal abscess).

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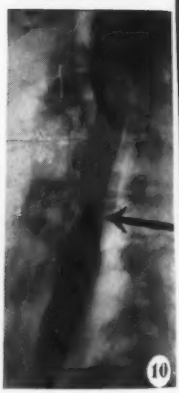

FIG. 6.—Lateral X-ray shows hold up of barium swallow, at upper end of œsophagus by an impacted large bolus of coherent masticated meat.

N.B.—Broadening of the sub-cricoid region of the œsophagus.

FIG. 7.—X-ray: lateral view of the cervical œsophagus showing a large retro-œsophageal abscess caused by impaction and perforation of the œsophageal wall four weeks previously, by a swallowed bone. The larynx is pushed forward. Œdema of the arytænoids can be observed. No bone can be observed now.

FIG. 8.—Impaction of a bolus of meat in the cervical œsophagus. Hold-up of the opaque swallow.

FIG. 9.—After removal of foreign body.

1. The barium swallow has not hitched up.
2. The sub-cricoid region is normal.

FIG. 10.—Oblique view of barium swallow, showing Carcinoma of œsophagus. (The discolouration above the obstruction is due to a faulty print.)

be palpated. The metallic cap was removed by incision through the posterior wall. Recovery was uninterrupted.

Comment.—This foreign body must have been driven through the posterior wall of the pharynx, through the " hernial ring "—the gap in the inferior constrictor of the pharynx, above the crico-pharyngeal sphincter, where the pharyngeal pouch originates.

Had the body not been radio-opaque its presence would never have been suspected, diagnosed or even sought. The importance of a routine X-ray after failure to find a foreign body by œsophagoscopy is obvious.

Perforation of the œsophagus by a pin; extrusion externally, through the chest wall.

In 1938, one of my post-graduate students related to me the following case.

An infant, aged 2½ years, attended with a " tumour " in the lower part of the chest, in the posterior axillary line.

On exploration, the point of a pin was found. Traction removed a tie-pin, 2½ inches long, very thin, sharply pointed, with a flat disc-shaped head, the size of a silver threepenny bit and with a sharp edge. It was lying within the thoracic cavity, and protruding between the ribs. The child made an uninterrupted recovery.

Subsequent enquiry elicited the fact that the father had last worn the tie-pin thirteen days previously, when the infant had been playing on the floor. He noticed that it choked and slight blood came away from the mouth. The infant remained quite well until the development of a swelling over the chest wall. When it swallowed the pin, the sharp point became impacted in the œsophagus and perforated through its wall. Gradually the entire pin point worked its way through, whence it migrated to the surface within thirteen days, without any suppuration or emphysema.

Comment.—Grey Turner (1946) records an analogous case of a kitten who swallowed a needle threaded with cotton. The kitten was ill for one week, and then a swelling appeared in the neck. In the centre of this was the needle and thread. Removal resulted in complete recovery. The needle and thread had perforated the wall of the œsophagus.

CASE 5.—*Delayed large retro-pharyngo-œsophageal abscess following an unsuspected perforation of the œsophageal wall by a bone impacted in the œsophagus.*

1948. Mrs. M., aged 50, attended out-patients' complaining of increasing dysphagia since swallowing a bone four weeks previously. The dysphagia had been worse for the past two days. She had a temperature of 100°. Mirror examination revealed a pool of pus in the hypo-pharynx. The X-ray (Fig. 7) shows in the lateral view a broadening of the retro-pharyngo-œsophageal space, with œdema of the arytenoids. The radiographic picture resembled that of a post-cricoid carcinoma. The antero-posterior view showed the trachea and larynx displaced to the left. The opaque bolus passed down rapidly and uninterruptedly, anterior to the swelling. There was no obstruction, and no radio-opaque foreign body was observed. The retro-œsophageal abscess was located by œsophagoscopy and aspirated through an opening in the posterior

wall of the œsophagus, and within three weeks she had made a satisfactory recovery.

Comment.—In this case the bone had perforated the wall of the œsophagus and infected the space posterior to it. The abscess here drained into the œsophagus.

Radiologically the case simulated a post-cricoid carcinoma.

A similar case was recorded by Asherson (1951).

Case of sudden, complete œsophageal obstruction due to impaction of a large bolus of meat.

Contrary to expectation, it is not only rigid bodies which become lodged in the upper œsophagus. A swallowed bolus, composed of masticated meat, if it is very large and bolted precipitately may become impacted in the cervical œsophagus, just distal to the crico-pharyngeus. It will then produce complete obstruction to swallowing, with drooling of saliva, and cough from overflow and aspiration of saliva into the larynx.

The foreign body can only be dislodged by manipulation through the œsophagus.

The following case records illustrate this.

CASE 6.—*Complete obstruction due to an impacted large bolus of soft meat in the œsophagus.*

A woman aged 40, while eating stewed steak, felt a portion " stick " in her throat at the level of the supra-sternal notch. For six hours she had been unable to swallow. The only physical sign was the presence of secretion of the hypopharynx, visible on mirror pharyngoscopy.

A lateral X-ray of the neck (Fig. 6) revealed a widening in the post-cricoid region, at which level the opaque meal was held up.

Under evipan anæsthesia, œsophagoscopy disclosed a mass of soft meat fibres tightly impacted in the post-cricoid region of the œsophagus. It was withdrawn in two bits. It contained no bone.

CASE 7.—*Complete obstruction due to impaction of a large bolus of soft meat.*

1932. A woman while eating suddenly swallowed a bolus of soft meat which " stuck " at the level of the sternum. This was followed immediately by pain, and great distress on attempting to swallow. Any attempt to swallow liquids or solids was impossible, everything being regurgitated immediately. This persisted for some hours. She was certain that the swallowed meat did not contain a bone.

The X-ray (Fig. 8) showed a hold-up of the opaque barium swallowed in the cervical œsophagus. No radio-opaque foreign body was visible. Under local anæsthesia, œsophagoscopy was performed. Just beyond the crico-pharyngeus a bolus of soft white meat was observed tightly wedged in. Attempts to withdraw it *en masse* or piecemeal with forceps proved futile. On pushing, the mass became dislodged and easily slipped downwards into the lower œsophagus. There was immediate and complete relief of the distressing symptoms.

Swallowing returned to normal. (Fig. 9)

CASE 8.—*Small foreign body impacted in a stricture producing œsophageal obstruction.*

A man aged 60 attended with sudden severe dysphagia following the

swallowing of an " orange pip." Œsophagoscopy showed the pip lodged in a stricture in the mid-thoracic region on account of an annular carcinoma (Fig. 10).

Though this carcinoma was discovered " accidently " in this way, thoracotomy revealed extensive inoperable growth spreading beyond the œsophagus, with adhesions in the aorta.

Summary

This paper deals with the unsuspected foreign body in the œsophagus and how it may produce prolonged dysphagia or pass through the œsophageal wall and be hidden in the prevertebral space.

The importance of anterior and lateral straight X-ray after the barium swallow is emphasised.

Cases are described of impaction by a soft bolus and of impaction of a small foreign body at a malignant stricture.

I am indebted to the Radiology Department, of the Central London, now the Royal National Throat, Nose and Ear Hospital (Sir Harold Graham Hodgson and Dr. T. V. Critchlow); of the Queen Elizabeth Hospital for Children (Dr. C. J. Hodson); and of St. Andrew's Hospital, Bromley-by-Bow (Dr. J. E. Wilson) for the Radiographs.

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FIBROUS DYSPLASIA OF RIB

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The more widespread use of mass radiography lends increasing importance and interest to the diagnosis and treatment of symptomless lesions of rib. Among such lesions is the condition of fibrous dysplasia, otherwise known as osteogenic fibroma or ossifying fibroma. Few publications on the subject are to be found in the British literature and the American literature is mainly from an orthopædic or a pathological point of view. It is for these reasons that the following cases of monostotic fibrous dysplasia of rib are considered worthy of description and discussion.

Case Reports

Case 1. George M., aged 56, was referred by his own doctor as a result of the discovery, on mass radiography, of a tumour of rib, possibly an osteogenic sarcoma. The patient stated that for the previous four months he had had pain like toothache round the left side of his chest. The pain was worse on bending forwards. Apart from this he was quite symptomless, and there was no history of trauma or other significant previous history. On examination the only positive findings were the presence of tenderness and a vague swelling over the posterior part of the seventh left rib. The radiograph revealed an elongated fusiform expansion of the rib just anterior to the angle (see Fig. 1). The radiographic density of the lesion was similar to that of normal rib and there was a vague cystic-looking pattern to be made out. Radiography of the remainder of the skeleton revealed no further lesions. Serum calcium, phosphorus and alkaline phosphatase showed normal values. Repeated search for Bence-Jones proteose in the urine was negative. Complete examination of the peripheral blood showed no abnormality.

A tentative diagnosis of solitary plasmocytoma or possibly an old fracture was made, and the lesion was excised, together with an inch of normal rib at both ends.

The pathological report was as follows:

Naked Eye (see Fig. 5). About 13 cm. of a rib expanded in the centre of the specimen by a fusiform tumour of smooth outline, reaching a maximum vertical diameter of 3 cm. as compared with 1·2 cm. of the major part of the rib. The growth has destroyed most of the bone but is clearly in itself osseous. The expansion, which has the characteristics of fibrous dysplasia, is situated along the course of the rib, immediately distal to the angle. One block taken transversely through the widest part of tumour and one along the mid-axis of the rib towards the angle to include the fairly sharp junction between the compact fibrous tissue of the tumour and the normal red marrow.

Histology (see Fig. 3). A bland, vascular and osteogenic fibrous tissue occupies and expands the medullary cavity. The new bone is of coarse-fibred type in widely separated islets. The rib cortex is porotic, and the widened marrow spaces are occupied by vascular processes from the medullary fibrous

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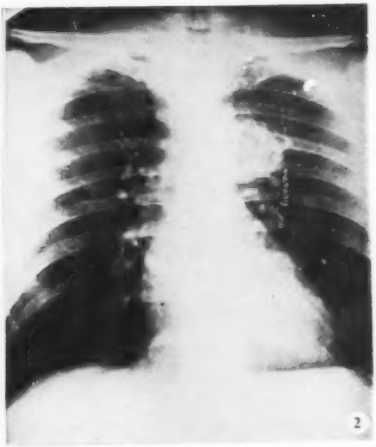

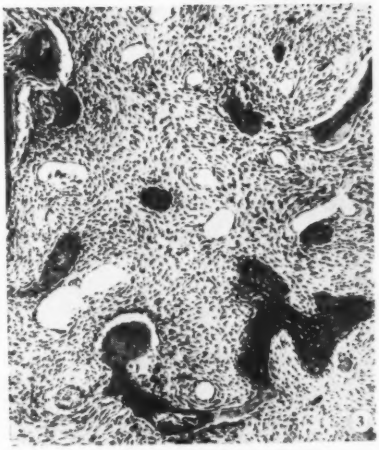

FIG. 1.—Radiograph of Case 1 showing fusiform expansion of rib.

FIG. 2.—Radiograph of Case 2 showing rounded trabeculated expansion of posterior end of rib.

FIG. 3.—Photomicrograph of Case 1 showing typical whorled fibrous tissue and well-marked trabeculæ of new bone.

FIG. 4.—Photomicrograph of Case 2 showing loose œdematous fibrous tissue and trabeculæ of new bone.

FIG. 5.—Specimen from Case 1 showing expansion of rib, thinning of cortical bone and uniform grey fibrous cut surface.

FIG. 6.—Specimen from Case 2 showing cut surface of retort-shaped lesion.

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tissue, which are, on the whole, less cellular than in the centre. In places where the periosteum has not been stripped, periosteal osteoblasts are rather prominent. Mitoses are not seen. This is a typical example of fibrous dysplasia.

CASE 2. Joseph I., aged 47, came to Thoracic Surgical Out-patients from the Orthopædic Department, where he had been referred by his own doctor with tumour of rib discovered on mass radiography. Apart from occasional aching medial to his left shoulder blade after hard work he was quite symptomless. Previous history and physical examination were negative. The radiograph (see Fig. 2) revealed gross expansion of the posterior end of the left fifth rib forming a rounded tumour-like mass traversed by thin bony trabeculæ. Penetrating radiographs suggested that the tumour was not attached to the vertebral column. Radiographs of the remainder of the skeleton were normal, and relevant blood chemical and cytological investigations were also normal. The diagnosis appeared to be between osteoclastoma and chondroma, but in view of the rarity of osteoclastoma in rib it was thought that chondroma was the more likely diagnosis.

The tumour was excised, some difficulty being experienced in separating it from the side of the adjacent vertebral body to which it was firmly attached despite radiological opinion to the contrary.

The pathological report was as follows:

Naked Eye (see Fig. 6). The specimen comprises about 20 cm. of a rib, from the inner concave aspect of which grows a large, smoothly outlined, egg-shaped tumour, 6·5 by 4 by 5 cm. of a fibro-cartilaginous texture. It has destroyed the rib from the inside of which it arises. The main tumour mass contains little if any bone. There is no degeneration centrally.

Histology (see Fig. 4). One section is taken across the expanded portion of the rib from which the " tumour " issues and shows osteoclastic resorption of the shaft on either side of the bland osteogenic fibrous tissue which occupied the medullary cavity. Some of the islets of new coarse-fibred bone are already being resorbed and are outlined by osteoclasts.

The convex dome of the " tumour " in the second section is covered with a thin, incomplete shell of bone, laid down in lamellæ by the periosteum. In this second section the fibrous tissue is much looser than within the rib and often myxoid in pattern.

This is an example of benign tumour growth from expansion of an intramedullary focus of fibrous dysplasia.

Discussion

Fibrous dysplasia of bone is not as yet a precisely defined condition, but it appears to occur in two forms. The first is in the polyostotic form sometimes associated with sexual precocity in the female and with areas of pigmentation in the skin. This syndrome is usually named after Albright, who described it in 1937 (Albright *et al.*, 1937). The second is the monostotic form in which endocrine abnormalities and skin pigmentation are absent. It occurs in order of frequency in rib, femur, tibia and upper jaw (Schlumberger, 1946).

The relationship, if any, between the foregoing conditions and other forms of fibrocystic disease of bone such as solitary bone cyst is not clear, and indeed there appears to be no very clear connection between the two forms themselves apart from their histological appearance. There is no evidence that the monostotic form progresses into the polyostotic form, and the absence of any endocrine manifestations in the monostotic type does not support the

belief that they are merely different stages of the same disease entity. The suggestion that the monostotic lesion is a congenital maldevelopment or a hamartoma seems a reasonable one. Originally the term hamartoma was defined by Albrecht as a tumour-like structure in which there is evidence only of an abnormal mixture of the normal tissue elements of the organ in which it arises. This definition would certainly seem to admit of a possible congenital cause for the lesion of monostotic fibrous dysplasia, but on the other hand the mere formation of new bone is no proof of congenital etiology, because metaplastic new bone is found in the normal repair process of a fracture. This leads to the suggestion that monostotic fibrous dysplasia may be a reaction to trauma, and indeed in Case 1, before any great thought about the diagnosis, the possibility of an old fracture was entertained. In the absence of a definite history of trauma the occurrence of a fatigue fracture of rib might seem feasible. Indeed, in many so-called cough fractures of rib there is often a history of cough, but absence of a history of a well-remembered spasm of coughing followed by a pain at the site of the lesion.

The histological picture of fibrous dysplasia is a relatively simple one showing a background of moderately vascular connective tissue which varies from tightly packed spindle-shaped cells arranged in whorls (see Fig. 3) to loose œdematous or myxomatous-looking tissue irregularly arranged (see Fig. 4). Superimposed on this background is a variable amount of trabecular new bone, and here and there a multinucleated giant cell may be seen. Certainly this picture appears to bear some resemblance to that of normal callus.

The radiological picture usually shows broadening or expansion of the bone (see Fig. 1), or even a rounded tumour-like projection from the side of the bone (see Fig. 2). There is thinning or erosion of the cortex, and there may be a multilocular or trabecular appearance very similar to that of osteoclastoma. However, from the differing radiological appearance of the two cases illustrated it seems unlikely that radiographs can be relied upon for the diagnosis of this condition.

Other special investigations are of little help; estimations of the serum calcium phosphorus and alkaline phosphatase should be performed to exclude hyperparathyroidism. The whole skeleton should be X-rayed, and in view of the fact that in the polyostotic form of fibrous dysplasia the lesions tend to be unilateral, special attention should be paid to the bones of the same side. The Wassermann reaction should be performed as a routine as for all bone lesions of obscure etiology.

Pathologically fibrous dysplasia shows no evidence of malignancy, but Coley and Stewart (1945) reported two cases of fibrous dysplasia in which sarcomata had developed with metastases. These cases were the only ones of undoubted malignant change that could be found in the literature. This small tendency to malignancy is rather unlike that of chondroma which has an undoubted tendency to sarcomatous change. Nevertheless even an apparently slight chance of malignant degeneration would seem to render complete excision of the lesion desirable when situated in a rib.

The only means of making a certain diagnosis is by histological examination, and in a rib this nearly always means complete excision of the lesion

rather than biopsy. However, if the condition of fibrous dysplasia is borne in mind, there is a fairly reasonable chance of making a correct diagnosis. Osteogenic sarcoma and osteoclastoma, although frequently mentioned, are particularly uncommon in rib. Multiple myeloma or the solitary plasmacytoma are of more frequent occurrence. Tietze's disease or the enlargement of the costo-chondral junction, which is sometimes painful, may cause confusion. Healed or healing cough fracture may present difficulties in view of similar radiological appearances. In addition to the conditions just mentioned differential diagnosis includes almost all tumours, inflammations and dyscrasias of bone.

Summary

Two cases of fibrous dysplasia of rib are described. The possibilities of endocrine traumatic and congenital factors in the etiology of the condition are discussed. The histological and radiological appearances are described, and it is suggested that awareness of the existence of this lesion in rib is the mainstay of the diagnosis. Excision of the lesion is recommended in view of the necessity of a histological diagnosis and also because of the possibility of malignant change.

I wish to thank Mr. J. S. Davidson for permission to publish these cases, Dr. D. H. Collins for the pathological reports, and Mr. P. Harrison for the excellent reproduction of the radiographs and photographs.

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PNEUMOPERITONEUM TREATMENT OF PULMONARY TUBERCULOSIS COMPLICATED BY PREGNANCY

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Women with pulmonary tuberculosis, who are being treated by artificial pneumoperitoneum (P.P.), can and do become pregnant. This paper deals with four such cases, three of which proceeded comparatively uneventfully during the pregnancy, although reinduction of the P.P. proved necessary after delivery. The fourth case, however, was complicated by the development of a right-sided spontaneous pneumothorax arising from the P.P.

Case Reports

Case 1. Pulmonary tuberculosis was diagnosed in this factory worker following a hæmoptysis in October 1946, when she was aged 20. There was bilateral upper zone infiltration, with a positive gastric lavage. Bilateral A.P.s were tried and failed. Nevertheless she improved, and by January 1948 her condition was regarded as quiescent.

In March 1949 she developed a spread of the disease in the left upper lobe, where there was a moderate-sized thin-walled tension cavity. She was treated by bed-rest alone, but there was little radiological change. In July 1949 it was discovered that she was four months pregnant. The pregnancy was allowed to continue, but it was decided to treat the cavity in the left upper lobe more energetically. The left phrenic nerve was crushed in August 1949, producing a good rise of the left hemidiaphragm, and a week later an attempt was made to induce a P.P. She was, however, very apprehensive about the procedure being carried out during her pregnancy, and after 250 c.c. air was introduced in the left subcostal region, the attempt was abandoned. She continued resting in bed, and the cavity appeared to close. (During her pregnancy also, her blood W.R. was found to be positive, and anti-syphilitic treatment was instituted.)

In December 1949 she gave birth to a live normal infant (although two weeks premature), and two days after her confinement a P.P. was induced. In April 1950 the left phrenic nerve was recrushed. The P.P. was maintained and she remained well, the left upper lobe cavity having closed completely, and laryngeal swabs were negative.

In November 1952 she became pregnant again. The P.P. was maintained until March 1953, the twenty-second week of the pregnancy, by which time the P.P. had almost completely absorbed. In September 1953 she had a normal confinement, giving birth to another live normal infant. The P.P. was not reintroduced after delivery.

Her condition at the time of writing was excellent.

Summary of Case 1. In the first pregnancy there was active cavitated

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disease in the left lung. An attempt at induction of a P.P. during this pregnancy failed, but it was successfully commenced two days after delivery. The P.P. was maintained uneventfully for three years, by which time the pulmonary disease was quiescent. The second pregnancy then occurred, and at the twenty-second week the P.P. was eventually abandoned, and not subsequently reinduced in the puerperium.

Case 2. Pulmonary tuberculosis was diagnosed in a housewife following the development of pain in the left chest in March 1951, when she was aged 27, and already had one child, aged 2. There was a small circumscribed cavitated lesion in the left lower lobe, and the sputum contained tubercle bacilli.

She was treated by bed-rest and " posture," as well as by chemotherapy (streptomycin and P.A.S.). In September 1951 her left phrenic nerve was crushed, producing a poor rise of the left hemidiaphragm however, and three weeks later a P.P. was induced. The lesion in the left lower lobe gradually contracted, and the cavity could no longer be seen on tomography. The P.P. was maintained.

In January 1952 she became pregnant. The P.P. was continued until April, 1952, the sixteenth week of the pregnancy, when it had to be abandoned owing to the exceptional enlargement of the uterus. It then became apparent that she had a twin pregnancy. She was not due for her confinement until October 1952, but she developed a toxæmia of pregnancy and required to be induced in September 1952, when she gave birth to live healthy twins, although a month premature.

Radiographs a week following the confinement showed the lesion in the left lower lobe to be slightly larger, and the P.P. was therefore reinduced on the eleventh day of the puerperium. It was maintained for a further year, and finally abandoned in September 1953.

At the time of writing her condition was excellent.

Summary of Case 2. A twin pregnancy complicated the P.P. treatment of a left basal cavitated lesion. The P.P. was maintained until the sixteenth week, when it had to be abandoned owing to the undue enlargement of the uterus. The P.P. was reinduced on the eleventh day of the puerperium.

Case 3. Pulmonary tuberculosis was diagnosed in this girl following the development of pain in the chest in June 1947, when she was aged 18. There was bilateral cavitated disease (most marked on the right), and the sputum contained tubercle bacilli.

The past history revealed the following facts: At the age of five months she had had anterior poliomyelitis, and was left with a paralysed right leg which necessitated her wearing a walking caliper splint. In 1944 she developed various neurological symptoms and signs, and by 1950 she presented a typical picture of disseminated sclerosis.

When the tuberculosis was confirmed she was treated by bed-rest, and a right A.P. was tried, but abandoned after six months. Nevertheless she appeared to improve, and her disease remained quiescent until June 1949. She then developed a tension cavity in the left upper lobe, and in January 1950 a P.P. was induced. Three months later her left phrenic nerve was crushed. The cavity appeared to close. The P.P. was maintained, but despite this she deteriorated, and a cavitated lesion now developed in the right upper lobe. She was given streptomycin and P.A.S., and this cavity also closed, but

there was still some active disease in the right lung. Since her condition was so unstable, and her disseminated sclerosis prevented consideration of more radical therapy, the P.P. was continued.

In November 1953 she was found to be four months pregnant. The effect of the pregnancy on her pulmonary disease, as well as on the disseminated sclerosis, was doubtful, but it was too late to interfere with the pregnancy. The P.P. was maintained until February 1954, the twenty-sixth week of her pregnancy. In May 1954 she gave birth to a live normal infant and she appeared to be well after delivery, no further manifestations of her disseminated sclerosis appearing.

In June 1954, however, a cavity appeared in the left apex, and she required to be treated with further chemotherapy, a left phrenic recrush and reinduction of the P.P.

Summary of Case 3. P.P. treatment did not control the tuberculous disease in the lungs, but it was continued, since alternative treatment was not feasible. When pregnancy developed, the P.P. was maintained until the twenty-sixth week. Three months after delivery there was a relapse of the tuberculous disease, and the P.P. was reinduced.

Case 4. Pulmonary tuberculosis was diagnosed in an unmarried Irish girl, following a period of general ill-health, in November 1951, when she was aged 32. There was bilateral infiltration, but sputum tests were negative for tubercle bacilli.

She was treated by bed-rest, " posture " and chemotherapy (streptomycin, P.A.S. and isoniazid), and in March 1952 a P.P. was induced. She made good progress, and in August 1952 she resumed her work as a waitress, the P.P. being maintained uneventfully with weekly refills (see Fig. 1).

On June 24, 1954 (*i.e.*, more than two years after the induction of the P.P.), she received her usual weekly refill of 1,000 c.c. air, the pressure readings before and after the refill being 5 cm. and 8 cm. water. While returning home from the Clinic she noticed some pain in the right chest together with breathlessness, but these symptoms lasted for a couple of hours only. When she next attended for a refill, one week later, she was screened and found to have developed a right-sided pneumothorax, while the P.P. was considerably reduced in size (see Fig. 2). It was decided to abandon the P.P. forthwith.

A fortnight later the P.P. was no longer visible, but the pneumothorax was still present, though smaller. She now had no symptoms referable to her chest condition, but she then divulged the fact that she had not menstruated for the five previous months. Examination revealed a gravid uterus, enlarged up to the level of the umbilicus. The pregnancy was allowed to continue.

Summary of Case 4. The P.P. treatment of bilateral pulmonary tuberculosis was complicated by the sudden development of a right-sided pneumothorax following a refill. It then transpired that the girl was twenty-four weeks pregnant. The P.P. was abandoned.

Discussion

There is still considerable difference of opinion with regard to the effect of pregnancy and confinement on pulmonary tuberculosis, ranging from the view that the course and prognosis of the tuberculous disease is not significantly affected (Friedman and Garber, 1946; Stewart and Simmonds, 1947),

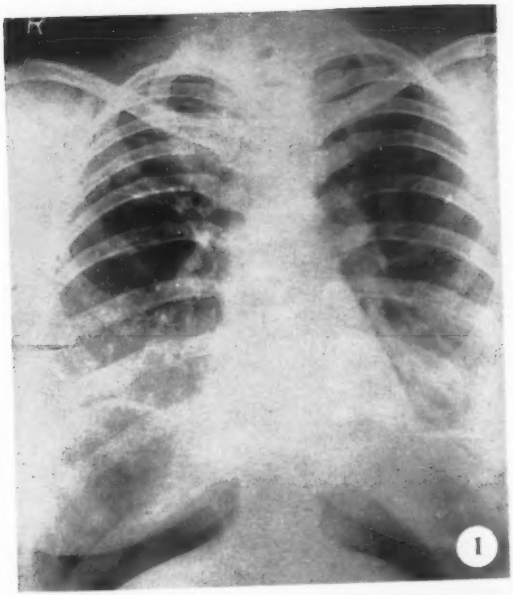

FIG. 1.—April 29, 1954, shows P.P. present.

FIG. 2.—July 1, 1954, shows right-sided pneumothorax to have developed, and P.P. smaller.

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to the view that there is a distinct risk of exacerbation of the tuberculous disease, especially in the first trimester and in the puerperium (Turner, 1950; Beven, 1952).

Similarly, varying views have been expressed about the use of P.P. therapy for women with pulmonary tuberculosis complicated by pregnancy. Banyai (1946), the originator of the treatment, did not offer any objection to the application of a P.P. in pregnancy, but Trimble *et al.* (1948) stated that pregnancy constituted a definite contraindication to its use.

When P.P. therapy was first introduced it was considered advisable to induce the P.P. soon after the confinement of a woman suffering from active pulmonary tuberculosis, on the assumption that the sudden descent of the diaphragm after delivery might be harmful to her pulmonary condition. In fact, Vajda (1937) advised the induction of a P.P. towards the end of term in order to prevent this descent of the diaphragm after delivery, and de Gouvea and da Silveira (1949) even recommended the induction of the P.P. actually during the course of labour itself, before the fœtus was expelled.

It is of interest that Cugell *et al.* (1952) have carried out pulmonary function studies (including measurement of the maximum breathing capacity) in pregnancy, and have found a small and variable degree of pulmonary collapse at full term, comparable to that seen during the P.P. therapy.

Doubt, however, has been expressed as to whether the P.P. is of value in these cases. Cohen (1946) pointed out that the diaphragm does not rise significantly in pregnancy until the seventh month, and, with the engagement of the head two weeks before term, the level of the diaphragm tends to fall. He considered that there was little advantage in inducing the P.P. until the abdominal muscles had recovered their tone three to four weeks after labour. Stewart (1951) found a slight but significant rise in the level of the diaphragm in the later months of pregnancy, and attributed this chiefly to the physiological changes of pregnancy similar to those responsible for the growth of the uterus. He also pointed out that, after a phrenic crush, some of the atrophy of the musculature of the diaphragm is permanent, and pregnancy stretches it further. Following delivery, there is no sudden or great change in the space relations of the lower thorax. The fatigued diaphragm would, in fact, be drawn up into the chest by the elastic recoil of the lungs, rather than fall suddenly. He did not therefore consider that there was any indication to establish or reinduce a P.P. immediately following delivery. He agreed, however, that a P.P. could be induced or maintained in pregnancy until the thirty-second week. Pagel *et al.* (1953) concluded: " It may merely add to the discomfort of a recently delivered woman to induce a P.P., for distension of the lax abdominal wall will be the main result."

There has been one case reported of a P.P. being induced in the presence of a pregnancy. Preminger (1952) described the case of an 18-year-old girl with advanced pulmonary tuberculosis, who had a P.P. induced without the knowledge that she was at the time, in fact, two and a half months pregnant. She made good progress, and the P.P. was maintained until the twenty-fifth week, when the level of the fundus was above the umbilicus, and technical difficulties arose with the refills. It was necessary to perform a Cæsarean at term, because of pelvic disproportion, and a live normal infant was born.

The mother's condition deteriorated post-partum, and four months later the P.P. was reinduced, with resultant benefit.

Very few reports have appeared of pregnancy complicating an already established P.P. Sahn and Bass (1950) described the case of a 28-year-old negress, who was treated by a right phrenic crush and P.P. After the P.P. had been maintained for fourteen months, she was found to be pregnant. The P.P. was discontinued at the twenty-fifth week, owing to discomfort following refills. It was found that the air absorbed more rapidly than before, and initial readings were lower. When the needle was inserted in the subcostal region, it was felt to rub the fundus even when the latter was only three finger-breadths above the umbilicus. The pregnancy was uneventful, and a Cæsarean was performed at the thirty-seventh week, on account of pelvic disproportion, and a live healthy infant resulted. The P.P. was not reinduced, and six months later she was well.

From the above, it is difficult to draw definite conclusions, but, from the experience gained in the cases described in this paper, it seems clear that P.P. therapy has a definite place in the management of pulmonary tuberculosis, both during pregnancy and in the period immediately following confinement.

Spontaneous Pneumothorax complicating P.P. Therapy

The development of a spontaneous pneumothorax during the course of P.P. treatment is uncommon, and was first reported by Mellies (1939), who described the case of a right-sided pneumothorax complicating a P.P. five months after its induction, and he ascribed this to a perforation of the diaphragm. Banyai and Jurgens (1940) described a similar experience, a year following the induction of a P.P., and postulated that the air travelled via one of the normal hiatuses in the diaphragm, into the posterior mediastinum, and so into the pleural cavity. This explanation was supported by Simmonds (1946). Further cases were reported by Sita Lumsden (1949) and by Wu and Neptune (1951), in which a right-sided pneumothorax occurred immediately after the P.P. was induced, and it was suggested that this was due to a patent pleuroperitoneal canal, a result of faulty embryological development of the diaphragm. Where there was only a potential communication, which was normally occluded by loose adherence of its walls, it required some excessive intra-abdominal pressure to force it open, and this would explain the sudden appearance of a pneumothorax some time after the P.P. was induced. Ross and Farber (1950) described three personal cases, and were able to collect a further twelve from California. Yannitelli *et al.* (1949) have recorded a fatal case in a boy, aged 16, in which there was a delayed development of a spontaneous pneumothorax in the course of P.P. treatment, and autopsy revealed a diaphragmatic rupture.

In the case described above (case 4), it is very possible that there was a potential congenital opening in the right hemidiaphragm, but there was no undue rise in the intraperitoneal pressure reading prior to the refill which was followed by the development of the spontaneous pneumothorax. Nevertheless, it is possible that the enlarging uterus did gradually raise the intra-

abdominal pressure, and this had the effect of opening up the pleuroperitoneal connection and so producing the pneumothorax.

The criterion of diagnosis in these cases is that, with the development of the pneumothorax, there is an associated loss of intraperitoneal air, since otherwise it is possible that a simple spontaneous pneumothorax has occurred, unrelated to the P.P.

When this complication arises in the course of P.P. therapy, no further attempt should be made to maintain or reinduce the P.P.

Summary

(1) Four cases in which pregnancy complicated the artificial pneumoperitoneum (P.P.) therapy of women with pulmonary tuberculosis are described.

(2) In three cases the P.P. was maintained until the sixteenth, the twenty-second and the twenty-sixth weeks of pregnancy respectively, the P.P. requiring to be reinduced immediately after delivery in two cases, and after three months in the third case.

(3) In the fourth case, however, there developed a right-sided spontaneous pneumothorax at the twenty-fourth week of pregnancy, due to leakage of air from the peritoneal to the pleural space via a congenital weakness in the diaphragm. This was probably due to raised intra-abdominal pressure associated with the pregnancy.

(4) The question of the relationship of pregnancy and P.P. therapy is discussed, and the literature reviewed.

(5) It is concluded that P.P. therapy has a definite place in the management of these cases, both during pregnancy and in the period immediately after confinement.

I should like to thank Dr. C. O. Edwards for allowing me to quote Cases 1 and 3.

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PERFORATION OF THE BRONCHIAL WALL BY A CASEOUS GLAND WITH ACUTE ASTHMATIC SYMPTOMS

By Desmond J. Leahy

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A case is presented of hæmatogenous dissemination of tuberculosis from a primary complex occurring in an adult, the glandular component of which is of great clinical significance.

Part of the gland penetrated the medial wall of the right main stem bronchus, causing symptoms of acute respiratory obstruction. It was later coughed up with immediate relief of symptoms.

The case is considered to be sufficiently unusual to be worthy of record.

Case Report

The patient, a female aged 23 years, was admitted to a Maternity Hospital in October 1953 in the sixth month of her first pregnancy with a diagnosis of hyperemesis gravidarum. In November she was found to have an intermittent temperature and in December an X-ray of her chest showed fine miliary mottling throughout both lung fields. She was transferred to a General Hospital, where the child was born.

In January 1954 treatment was commenced with Streptomycin 1 gramme daily and P.A.S. 4 grammes six-hourly.

In February 1954 she developed a right pleural effusion, and in March she was transferred to this hospital, where treatment was continued with Streptomycin 1 gramme daily and isonicotinic acid hydrazide 100 milligrammes twice daily.

In April she developed a fluctuant swelling in the sacral region, which proved to be a tuberculous abscess. There was no X-ray evidence of a bony lesion. The abcess was aspirated and yellow fluid obtained. Culture was positive for tubercle bacilli. Following this hæmatogenous dissemination it was decided to increase the dose of isonicotinic acid hydrazide to 300 milligrammes daily. At this time examination of the cerebro-spinal fluid gave a normal result, full blood examination was normal and the blood sedimentation rate was 43 mm. in one hour (Wintrobe).

In May she was found to have an enlarged glandular mass in the inferior deep cervical group measuring 3 inches by 1 inch.

Asthmatic Attack. In July there was a rather sudden onset of respiratory distress with wheezing respirations and gradually increasing dyspnœa. Loud rhonchi were heard over both lung fields, and as she gave a history of a somewhat similar but much less severe attack shortly before, she was treated as a case of asthma. Her condition worsened, cyanosis increasing. She was coughing a good deal during this attack but was unable to bring up any sputum. After some hours of respiratory difficulty she suddenly coughed up a solid piece of

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caseous material of cylindrical shape about 20 mm. by 10 mm. by 10 mm. in size. Her symptoms of respiratory obstruction and cyanosis were dramatically relieved. She was now bringing up a lot of mucoid sputum which continued for the next twelve hours and then her chest was quite clear of all adventitia. It should also be mentioned that the patient did complain of a dull pain in the right upper chest which became more acute after taking a deep breath. The pain was especially marked when she tried to breathe out following a deep inspiration. She also had a feeling that there was something lodged in her chest which she was unable to move by coughing.

Bronchoscopy was now performed and the following condition was found. The right main bronchus was narrowed by an irregular granular mass in the medial wall half an inch below the carina. This looked very much like a carcinoma. The bronchoscope could not be passed beyond the swelling. At one or two places caseous points appeared through the reddened granular surface. Biopsy was performed and the report is given below. A week later a further bronchoscopy was carried out. This showed the carina to be thickened, and there was a granular mass on the medial wall of the right main bronchus which was ulcerated, and caseous material was more prominent than previously. As much as possible of this caseous material was sucked out. Following this second bronchoscopy and partial evacuation of the obstruction the patient was much relieved, and the pain in the upper right chest and feeling of obstruction had now almost disappeared.

Pathological Report

Specimen: Object coughed up by patient. A smooth, rather soft whitish mass, 2 by 1 by 1 cm., mottled with black pigment. On section it has a cheesy consistency and shows pigment deposits throughout.

Microscopic examination showed a structureless mass of necrotic tissue, containing deposits of carbon pigment and small areas of calcium deposition. Round the edges there is an infiltration of polymorphs into the necrotic tissue. This is caseous tissue and probably represents a caseating lymph node.

No acid-fast bacilli seen in sections.

Bronchoscopic biopsy. Report: Microscopic examination showed caseous necrosed tissue and tuberculous granulation tissue with included bronchial mucous glands.

Anatomical Observations

The regularity and position of the hilar lymph nodes was pointed out by H. P. Nelson (1932). One of the largest of these glands lies in the angle of the bifurcation of the trachea, the greater part of the node lying in contact with the medial surface of the right main stem bronchus. It was probably this node which penetrated the medial aspect of the bronchus in the case under discussion.

Sites of Perforation

Paunz (1932) stated that perforation was most often found on the medial wall of the right main bronchus. Auerbach (1944) reported on 1,656 autopsies in which he found 22 perforations. In his series he found that perforations occurred most frequently in the area of the carina, but that the distribution was fairly equal between the trachea, the right and left main stem bronchi.

Discussion

This case may be regarded as a hæmatogenous dissemination of tuberculosis from a primary complex, occurring in an adult.

The miliary spread in the lungs, the pleural effusion, the subcutaneous abscess and the prominent glandular element point to this conclusion.

The marked enlargement of the tracheal and tracheo-bronchial glands was well shown by tomograms. It was hoped that the penetration of the right main bronchus by the caseous gland would be seen in the tomograms, and although this was suggested in one cut it was not conclusive.

It is probable that the enlarged lower deep cervical group of glands was due to a direct extension from the tracheal group.

It is interesting to note that it is the large glandular element which has remained and has been responsible for the complications which have developed in this case. One's attention is thus drawn to the importance of the glandular component of the primary complex.

Penetration of a bronchus by a caseous gland which causes acute respiratory distress is uncommon in adults but is not so uncommon at younger age periods. Lowys, Tison and Le Barre (1948) report an interesting case in which rupture of a caseous tracheo-bronchial gland occurred in a child, sudden death occurring from asphyxia due to caseous material entering the trachea. A second similar case is reported by Lowys, but in this case the child recovered. A cavernous tracheo-bronchial gland was beautifully shown by tomography.

There are, however, some cases reported at later age periods. Brun and Viallier (1948) report two cases of bronchial perforation by hilar glands, one at the age of 17 years and the other at 20 years of age. There is also a case reported of multiple perforations of the trachea and bronchus simultaneously by cervical and hilar glands in a man of 40 years. Boucher and Ferrand (1948).

Although it is rare for an adult to cough up a caseous gland, there are numerous examples of broncholiths being coughed up, and it is interesting to note that these have been reported in very early medical literature; thus Galen and Aretaeus, of Cappadocia, reported cases of cough with expectoration of stones. Alexander of Tralles reported the history of a man who coughed up stones so large that they made a noise when they struck the ground (Poulalion, 1891).

Head and Moen (1949) report a series of ten cases in which calcium stones or plaques were coughed up by patients. These cases were complicated by hæmoptysis, atelectasis, lung abscess, recurring pneumonitis and broncho-œsophageal fistula. Severe pain was also a feature of some of these cases, the severe pain being referred to by some writers as bronchial colic.

The pain which occurred in our case was almost certainly of a similar nature, and was probably due to bronchial spasm. The patient when questioned on the subject of pain distinguished two forms. A dull ache or sense of discomfort in the right upper chest was present almost continuously, and this was associated with a feeling of something lodged in the chest which could not be got rid of by coughing. The other type described was a sharp pain which occurred in the expiratory phase of respiration and was especially marked on deep breathing.

PLATE VI

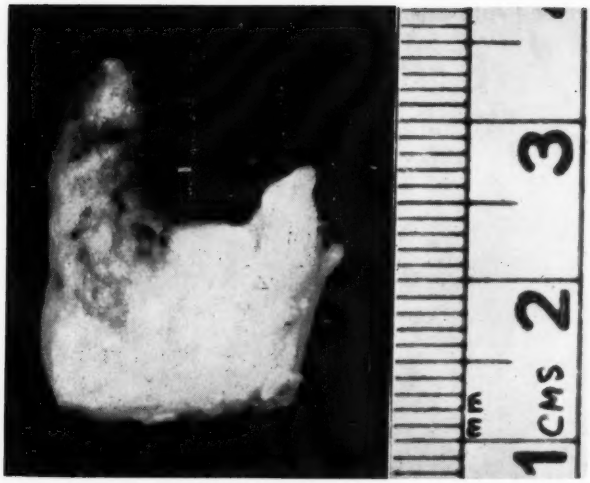

FIG. 1.—Large piece of caseous gland coughed up by patient.

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The localisation of the pain by the patient is interesting. As we know the exact site of the perforation in the bronchus it is interesting to note the area of the chest wall to which the pain was referred. The site of the pain was exactly located by the patient in the second right intercostal space 3 inches from the midline. It radiated along the intercostal space to the axilla. It would thus seem that the pain was referred from the bronchus to the area of skin supplied by the second dorsal segment.

It should be noted that this asthmatic type of attack described above is a condition to be borne in mind when a patient develops respiratory distress of sudden onset. Early bronchoscopy may be a useful and indeed an essential procedure in such a case and can bring dramatic relief.

Summary

A case of hæmatogenous dissemination of tuberculosis from a primary complex occurring in an adult is described. Attention is particularly drawn to the glandular component of the complex, which in this case was of considerable size and gave rise to important clinical symptoms.

The sudden onset of an attack of acute respiratory distress is recorded. This was due to bronchial obstruction caused by a caseous hilar gland which penetrated the right main stem bronchus. Attention is drawn to the place of bronchoscopy in such an attack.

The type of pain which occurred is described and its possible causation and localisation are discussed.

My thanks are due to Dr. J. E. Geddes for his encouragement and permission to record this case. Also to Dr. H. J. T. Ross for very helpful advice; to Dr. D. J. O'Brien who reported on the pathological specimens; and to Mr. S. J. MacHale, Mr. S. F. Stephenson and Mr. Roy who kindly carried out the bronchoscopies.

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ADDENDUM

Since writing this article the patient coughed up a further large piece of caseous tuberculous gland, (see Fig. 1.)

On this occasion the piece of gland came up easily and there was no asthmatic attack.

PULMONARY ADENOMATOSIS (ALVEOLAR CELL TUMOUR)

A CASE WITH AN UNUSUAL CAVITATING LUNG LESION

By G. B. Rooke

From Bevendean Hospital, Brighton

Pulmonary adenomatosis (alveolar cell tumour) is not usually a cavitating lesion.

The clinical course is as a general rule recognised to be a short one.

The following case here recorded is an exception to the general rule.

A housewife aged 35 came under observation in July 1951 with the following history:

Her mother had died of carcinoma (? site) in 1934. Her sister died in 1934 of pulmonary tuberculosis.

The patient had had scarlet fever and measles in early childhood with occasional bouts of bronchitis since. Some shortness of breath on exertion had been noticed since 1938, but this had become worse in 1951. In May 1951 the left side of her chest had been hurt in a fall and shortly afterwards she had produced a bloodstained sputum. There was no loss of weight and no pain, but she continued on various occasions to produce stained sputum.

Her first chest radiograph in July 1951 showed an irregular fluffy opacity in the left mid-zone covering an area about 4 inches in diameter; there were also small irregular areas of calcification in the right upper zone. Series of radiographs over the next few months showed little change in the original picture. Tomograms of the left lung showed numerous small cavities in the area of opacity. A lateral film showed the shadow to be in the superior segment of the lingula.

Diagnosis of pulmonary tuberculosis was made and she was treated for three months in hospital with bed rest and a course of Streptomycin with P.A.S. A course of Aureomycin was also given. Her sputum was persistently negative for tubercle bacilli and chemotherapy produced no change in the radiographic appearances.

Bronchoscopy in January 1952 revealed no abnormality. A bronchogram of the left lung in February 1952 showed marked bronchiectasis of the anterior segmental bronchus of the left upper lobe. All other branches of the left bronchus appeared normal. At this time (February 1952) her weight was 9 stone 8 lb. Pulse and temperature were normal, white cell count 8,100, hæmoglobin 104 per cent. There was only a trace of sputum containing pus and epithelial cells and from this a mixed bacterial flora was grown, including pneumococci and hæmolytic streptococci. No tubercle bacilli were found. The only abnormal physical signs were a few rhonchi and râles over the left

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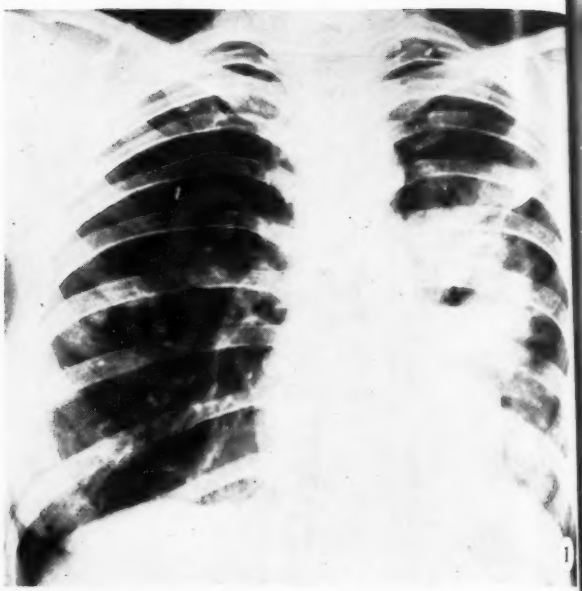

FIG. 1.—P.A. chest film, 25.1.54, showing cavitating lesion with fluid level in the left mid zone and small rounded foci in the right lung field.

FIG. 2.—Left lateral tomogram 9 centimeter cut, 1.2.54, showing cavitation in all areas of infiltration.

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chest anteriorly. The patient was discharged to her home with a diagnosis of bronchiectasis at the end of February 1952.

Further chest films showed considerable extension of the shadowing in the left lung. By October 1953 the apex of the left lower lobe had become involved and some small opacities had appeared in the right mid-zone. Bronchoscopy was again performed and revealed no abnormality. A further left bronchogram showed no new areas of bronchiectasis and no bronchial block was demonstrated. A second trial of Streptomycin and P.A.S. had no effect on the radiographic appearances.

By January 1954 the apico-posterior segment of the left upper lobe had become involved, with cavitation, and there was a multi-loculated cavity in the apex of the left lower lobe. Her general condition at this time was surprisingly good. The chief complaints were of pain beneath the left scapula and of cough with copious watery sputum. She had lost 5 pounds in weight since February 1952. She remained afebrile, the white cell count was 8,800, of which 10 per cent. were eosinophils. Hæmoglobin and red cell counts were normal, sedimentation rate was sixteen (Westergren), and the Wassermann reaction was negative. Neither excess fat nor parasites were found in the stools. She was coughing up two cartons full of mucoid sputum in twenty-four hours; no tubercle bacilli or malignant cells were found. Culture for fungi produced *Candida albicans*. The amount of sputum increased when she altered her position. A specimen of fluid was obtained direct from the cavity in the apex of the left lower lobe by lung puncture. This showed cell clumps consisting of neutrophil leucocytes and cells described as being similar to those found in serous fluids called " endothelial cells." Bizarre nuclear forms and mitotic figures were not seen. Culture produced scanty growth of non-hæmolytic streptococci, no tubercle bacilli were seen and prolonged culture for fungi produced *Aspergillus niger*.

Lung biopsy at the end of February 1954 was reported upon as follows:

" Section of tissue taken from the apical segment of the left lower lobe show distended thin-walled alveoli filled with histiocytic cells. Sections of tissue from the posterior segment of the left upper lobe show glandular structures lined by mucoid columnar epithelium. In the alveoli there is an exudate of polymorphs and histiocytic cells. *Diagnosis:* Adenomatosis of lung (alveolar cell tumour)."

The patient died in June 1954 aged 38, three years all but a month after a lung lesion was found. No post-mortem examination was made, so that the diagnosis depends on the biopsy result.

Discussion

Unusual features in this case appear to be:

The radiographic picture which differs from the usual description of alveolar cell tumour.

The radiographic appearances in the early stages are usually miliary, the nodules being of unequal sizes. As secondary infection supervenes the nodules appear to coalesce and large segmental atelectases develop. In the present case the first lesion seen in 1951 was about 4 inches in diameter and the only

small opacities developed later in the right mid-zone. Cavitation was seen in tomograms of the original lesion as early as February 1952, and all the succeeding lesions in the left lung showed cavitation. Cavitation is rarely mentioned in other cases of alveolar cell tumour.

2. The length of survival from the first finding of the lesion in 1951.

Fisher and Holley (1953) describe five cases of alveolar cell carcinoma, four of whom were dead within three months of the onset of symptoms and the fifth in ten months. They state that the clinical course is much shorter than in other cases of untreated malignant pulmonary neoplasms.

Fisher and Holley (1953) subscribe to the theory that the so-called alveolar cell tumours do not arise from alveolar epithelium, but that they originate in the terminal bronchiolar epithelium. Anderson and Pierce (1954) describe a variety of squamous bronchial carcinoma in which a thin layer of malignant cells grows into and lines a pre-existing cavity. Was the cavitation in this case due to some other cause, such as fungal infection, and did the columnar mucoid epithelium found in the biopsy specimen grow in at some later date? The copious mucoid sputum was a late feature, and it may be that its onset marked the appearance of the new secretory cells.

Summary

A case of pulmonary adenomatosis, with unusual features of (*a*) cavitation and (*b*) a prolonged survival rate since discovery of the lesion, is recorded.

My thanks are due to Dr. F. E. de W. Cayley for his advice, and to Mr. A. M. Macarthur for the loan of the biopsy specimens.

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REVIEWS OF BOOKS

A Practical Manual of Diseases of the Chest. By MAURICE DAVIDSON. Oxford University Press. 1954. Pp. 658. 261 illus. Price 84s. Fourth edition.

Dr. Maurice Davidson is to be congratulated on the publication of the fourth edition of his well-known textbook on Diseases of the Chest. Considerable additions have been made to our knowledge of respiratory disorders since the last edition was produced, necessitating extensive revision of the sections dealing with the pneumonias, and the treatment of bronchiectasis, pulmonary tuberculosis, and other infective diseases. In the preparation of this edition Dr. Davidson has been assisted by Dr. John Friend. This book is well written, well produced, and, although heavy to hold, easy to read. The information is reliable and authoritative, and the clinical aspects of the diseases are fully emphasised, as would be expected from a physician of such wide and mature experience.

Dr. Davidson has jettisoned much of the material which has become outmoded, but he still retains his affection for the leech as a therapeutic agent in pneumonia. X-ray shadows seen in the region of the right cardio-phrenic angle often lead to considerable difficulties in diagnosis, and space might have been found for a description of some of their causes, such as the harmartoma and the pleuro-diaphragmatic or "spring-water" cyst, both of which are liable to be mistaken for bronchial carcinoma. In certain cases of rheumatoid arthritis the lung fields, as revealed on X-ray examination, show widespread reticulation and nodulation, characteristic of the so-called rheumatoid lung disease. The significance of these appearances on X-ray films is not always appreciated, and they are worthy of mention in a textbook of this size. The results obtained by the administration of Cortisone in cases of "status asthmaticus" are so remarkable as to warrant inclusion, and striking improvement often follows Cortisone therapy in sarcoidosis, an observation which argues against the view, which is still sometimes held, that the disease is related to tuberculosis.

I have much enjoyed reading this new edition; the various case reports add considerably to the interest and value of the work, and the illustrations throughout are of a high standard. This textbook can be confidently recommended to the student preparing for the higher examinations, and, as a book of reference, to the chest specialist.

G. E. BEAUMONT.

The Anatomy of the Bronchial Tree. With special reference to the surgery of lung abscess. By R. C. BROCK. London: Oxford University Press, 1954. Pp. 250. 286 illus. Price 45s.

The second edition of *The Anatomy of the Bronchial Tree* will be as welcome to all students of diseases of the chest as was the first, which appeared in 1946. Since then this book has become established as an essential textbook in the field of pulmonary disease.

Since 1946 the importance of segmental anatomy has increased enormously, for at that time segmental resection was a rare operation, whereas today it is one of the commoner procedures in the surgical treatment of pulmonary tuberculosis. On the other hand, largely owing to the use of the

antibiotics, the whole picture of lung abscess has completely changed. In the earlier half of the past decade the drainage of a lung abscess was a common operation; today it is a rarity, and as the author himself says: " Some authorities are so bold as to say that surgical drainage should never be used."

Despite these changes the author feels justified in using " Lung Abscess " as a peg on which to hang clinical descriptions of disease as it affects individual segments. The excellence of the material, and in particular of the radiographs, warrants this view, but to include extensive and detailed descriptions of the surgical approach to abscesses in each segment seems difficult to justify even on the grounds that " it may be useful anatomical exercise." Probably this book, otherwise almost beyond reproach, would be even better if these sections were excluded.

The Standard International Nomenclature is used throughout, and a chapter is devoted to the history of the development of this terminology. Valuable additional material based on the more recent work of Boyden has been added to the subject of bronchial variants and anomalies, and due attention has been paid to the vexed " Lingula-Anterior Segment " problem. An appendix deals with the preparation of bronchial casts and the technique of injection of segments, more illustrations have been added to the earlier addition and the main text of the book has been modified where necessary

The new edition like its predecessor will appeal to all interested in pulmonary disease, whether physician or surgeon.

J. R. BELCHER.

B.C.G. and Vole Vaccination. A Practical Handbook. By K. NEVILLE IRVINE. London: N.A.P.T. 1954. Pp. 96. 10 illus. 12s. 6d.

B.C.G. vaccination in this country has, so far, been offered to special groups, such as close contacts of tuberculosis cases, medical students, nurses and school leavers, because of the special risks attendant on them, but as the initial cautious attitude towards vaccination gives way to increasing confidence in its safety and efficacy in providing a measure of immunity, it may be expected that there will be a trend towards total vaccination of all tuberculin-negative reactors.

The timely publication of this pocket-sized, practical handbook will be welcomed by doctors, health visitors, nurses and medical students who may be concerned with this work for the first time and the information, especially regarding statistics, should be helpful in providing the facts when offering vaccination.

All the relevant historical data, together with the practical details of tuberculin testing and B.C.G. vaccination, have been gathered together in a small compass and presented simply and lucidly; further possible lines of investigation and modification are indicated, and some suggestions are made for simplifying the procedure when mass vaccination is done. The coloured plates illustrate well some typical reactions following tuberculin testing and vaccination by different methods.

J. H. P. JOHNSON.

Transactions of the 13th Conference on the Chemotherapy of Tuberculosis. St. Louis: Veterans Administration Area Medical Office. 1954. Pp. vi + 442.

This is the 13th Conference in eight years held by the Veterans Administration. It marks another stage in the evolution of the chemotherapy of

tuberculosis and of views which are changing with experience of the original drugs, and of others more recently introduced and now under trial in the laboratory and in clinical practice.

In America much of the original clinical work on antibiotics in tuberculosis was done in the Veterans Administration hospitals and met with justifiable criticism in this country on the grounds of absence of proper controls. That criticism no longer applies and these Transactions cover a wide field of valuable investigation. The programme of one conference is linked with those of preceding conferences, and investigations and follow-up studies are continuous. Views on the early drugs, Streptomycin and PAS, are now well defined, and the place of Isoniazid, alone and in combination, is fairly well determined.

Many papers deal with problems of resistance and cross-resistance to these drugs, and a section is devoted to a discussion of the action of some derivatives and analogues of Isoniazid and of certain substituted Diphenyl Thioureas. Interest has been reawakened in the thiosemicarbazone analogue Pyrazinamide and several papers establish a claim for the careful use of the drug in combination with Isoniazid.

There is a full discussion of the treatment of miliary tuberculosis and tuberculous meningitis, and there is agreement on the value of including Isoniazid in the treatment régimes. Evidence is given in favour of a combination of Streptomycin, by intramuscular injection, with Isoniazid and PAS and the discontinuance of intrathecal injections

The papers on surgery in pulmonary tuberculosis are based on adequate preparation of the patient by treatment with appropriate drugs; opinion favours a prolonged period of treatment on these lines and makes surgery a question of removing, or otherwise dealing with, residual lesions. The majority of the papers deal with types of resection and with the bacteriological examination of the excised tissues. It it refreshing to find one paper pleading timidly for a wider outlook and for fitting the treatment to the patient, and not forgetting the value of the relaxation methods.

In a section dealing with laboratory studies there is a paper on problems of immunity in certain non-tuberculous infections in relation to treatment by antibiotics, the lessons of which are tentatively applied to tuberculosis. This paper is based on careful and thoughtfully executed work and deals with an aspect of antibiotic treatment which is of fundamental importance in tuberculosis.

It is impossible in a brief review to do justice to so many communications, which cover so many problems. One can only pay tribute to the organisers of the conference, and to the work of the many contributors and to those who who took part in the many discussions. The transactions are a useful work of reference.

CHARLES CAMERON.

Die Narkose: Ein Lehr- und Handbuch. By H. KILLIAN and H. WEESE. Stuttgart: Georg Thieme Verlag. 1954. Pp. 1,003. 412 illus. D.M. 170.

Medicine in general and anæsthesia in particular have suffered a loss in the death early this year of Professor Weese. In 1932 Weese laid the foundations of modern anæsthesia by his work on the short-acting intravenous barbiturate "Evipan." *Die Narkose*, a book written in collaboration with Professor Killian, is a fitting memorial to a great pharmacologist. Together with another posthumous publication on an even shorter-acting barbiturate (Koss and Weese, 1954), this book should ensure that Weese's name is not forgotten.

Die Narkose is described by the authors as a handbook, but it is more a reference work than a practical guide to the administration of anæsthesia. Its thousand pages contain a history of anæsthesia, a section dealing with the theories of narcosis, and a most exhaustive account of the physiology and pathology associated with the administration of almost all known anæsthetic drugs. Much of the mass of information given in the text is also presented in the form of well-chosen graphs and diagrams.

A comprehensive list of references is given at the end of each chapter and the impression is gained that parts of the book dealing with modern techniques are more of a review of recent publications than a description of first-hand experience. This is especially true of the sections devoted to anæsthesia for thoracic surgery. The cardio-vascular and respiratory disturbances of the open pneumothorax and the use of intermittent positive pressure to control them are well described, but of methods of anæsthesia for pulmonary resection and cardiac surgery there is an inadequate account. In particular there is no mention of the sequence of thiopentone, nitrous oxide, oxygen, curare and pethidine, so popular in this country for thoracic cases.

Despite discussion of the indications and contra-indications of the various anæsthetics the reader is left bewildered by the multiplicity of methods available without any clear lead as to the one of choice.

These criticisms do not detract from the value of the book as a reference work. *Die Narkose* is excellently arranged, printed and produced, and it is to be hoped that an edition in English will become available.

B. A. Sellick.

Antibiotika-Fibel. Indikation und Anwendung der Chemotherapeutika und Antibiotika. A Synopsis of Antibiotics. By A. M. Walter and L. Heilmeyer. Stuttgart: Georg Thieme Verlag. 1954. Pp. viii+183. Tables and Figs. D.M. 79.

Professor Heilmeyer introduces this expensive little book by saying that the literature in regard to antibiotics and chemotherapy as a whole has reached the infinite and can no longer be encompassed by one individual alone. It appeared essential, therefore, to crystallise, as far as possible, the information which possesses practical application and deliver into the hand of the physician a companion calculated to be of immediate assistance.

The volume thus endowed promises to live up to this claim. It is exceedingly well produced and thought out. An introductory chapter discusses the development and the most recent pharmacological views of chemotherapeutic agents such as the sulphonamides, penicillin, streptomycin, the tetracycline groups chloramphenicol, eythromycin, carbomycin, bacitracin, polymyxin, neoviomycin and fumiagillin.

The major parts of the book are, however, devoted in a systematic fashion to the chemotherapy of infectious diseases of every type including tropical diseases, and are most thorough. The symptoms and signs are carefully tabulated and all recognised forms of therapy are listed, with dosages, in the order of merit. The side-effects are clearly stated, and this in particular in the chapter discussing the chemotherapy of tuberculosis. Here much is still said in favour of the thiosemicarbazones, but their value is critically analysed and the dangers emphasised. On the whole the style is simple and easily followed and the synopsis of the tables makes this an easy reference work.

It is sad, however, to note that Yatren, Emetine and Chloroquin feature

in equal length in the chapter on Amœbiasis, and very little reference is made to the modern British anti-malarial drugs.

While the literature is international the references which follow each chapter suffer very often by incompleteness, such as absence of initials, suggesting that the workers referred to may not be known to the authors by their original papers.

Apart from these minor criticisms this book deserves wide study.

LEON CUDKOWICZ.

Ergebnisse der gesamten Tuberkuloseforschung. By H. BEITZKE, ST. ENGEL, L. HLEIMEYER, J. HEIN, E. UEHLINGER. Stuttgart: Georg Thieme Verlag. 1954. Vol. XII. Pp. viii+488. 98 illus. D.M. 65.

This book by eleven contributors is the twelfth volume in a series dealing with the results of investigation into tuberculosis. The editors' intention has been to clarify debatable problems by a critical approach.

The first three chapters deal with the effect of perforation of tracheobronchial glands during the various stages of pulmonary tuberculosis. This condition has recently gained much attention on the Continent through the work of Schwartz. Engel thinks that it is of less significance in European countries than in Turkey, where Schwartz did most of his investigations. His views are shared by Dufourt and Depierre, who contribute a stimulating chapter on the clinical findings. Using bronchoscopy, they were able to demonstrate perforation of fistula-formation of a gland into a bronchus in a number of their patients (mainly children and young adults), even in the absence of clinical signs and symptoms. The late Professor Beitzke gives a lucid, highly critical and yet objective account of the pathology of perforation of tracheobronchial glands.

Wurm supplies a chapter on "Tuberculosis and Atelectasis" based on the results of his wide pathological investigations. His discussion of the part played by " peri-cavernous atelectasis," both in the enlargement and closure of cavities, deserves special attention. Mai, in a critical article on " Asthma and Pulmonary Tuberculosis," agrees with the view currently held in this country that there is no inter-relationship between the two conditions, either in childhood or in adult life. Schäfer, in an exhaustive study of " Tuberculosis and Endocrinology," shows the significance of the endocrine system in the problem of tuberculosis and its possible influence on the course of the disease. His statement that, in spite of its inherent risks, high dosage Vitamin D therapy has its place in the treatment of pulmonary tuberculosis would not be fully accepted in this country. Wetzel writes on tuberculosis of the spleen reviewing fourteen of his own cases in about half of which the diagnosis was made before death. The last two chapters are supplied by Spiess writing on " Problems of B.C.G. Vaccination " and by Vogt on the " Influence of Superinfection on the course of Tuberculosis in Childhood."

The work throughout is of a high standard and is based on the authors' experiences. The book is beautifully printed and produced and both illustrations and reproductions of X-rays are of the highest order. There is a very extensive bibliography and, as a source of reference, the work should be a valuable addition to the library of all those interested in the problems of tuberculosis.

L. ZONDEK.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues:

The Brompton Hospital: The story of a great adventure. By Maurice Davidson and F. G. Rouvray. London: Lloyd-Luke (Medical Books) Ltd. 1954. Pp. 152. 31 illus. Price 21s.

Chemotherapy in the Treatment of Tuberculosis. Eleven papers read at a Tuberculosis Educational Institute Refresher Course, Cambridge 1953. London: National Association for the Prevention of Tuberculosis. 1954. Pp. 60. Illus. Price 5s.

The Human Side of Tuberculosis 1953–1954. Annual Report of the National Association for the Prevention of Tuberculosis of Great Britain. London: N.A.P.T. 1954. Pp. 72.

Physiology in Diseases of the Heart and Lungs. By M. D. Altschule. Harvard University Press (London: Geoffrey Cumberlege). 1954. Pp. x + 554. Price 60s.

Registrar-General's Statistical Review of England and Wales for the year 1953. Tables. Part I. Medical. London: H.M. Stationery Office. 1954. Pp. 365. Price 10s.

Technique and Results of Fluoroscopy of the Chest. By E. A. Zimmer (Trs. E. W. Loos). Illinois: Charles C. Thomas (Published British Commonwealth: Blackwell Scientific Publications). 1954. Pp. xiv + 135. Price 40s.

Clinical Physiology of the Lungs. By C. K. Drinker. Oxford: Blackwell Scientific Publications. 1954. Pp. ix+84. Illus. Price 40s.

Derbyshire County Council. Annual Report of the County Medical Officer of Health for the year 1953. Heanor, Derbyshire: Arthur Gaunt and Sons. 1954. Pp. 139.

Northern Ireland Tuberculosis Authority. Eighth Annual Report for the year 1953. Pp. 68.

Traitement de la Tuberculose Pulmonaire. By Jean Paraf, Pierre Zivy and Madeleine Paraf. Paris: Masson et Cie. 1954. Pp. 212. 3 Figs. Price 950 fr.

Primo-Infection et Réinfection dans la Tuberculose Pulmonaire. By Georges Canetti. Paris: Éditions Medicales Flammarion. 1954. Pp. 272. 32 illus. Price 2,375 fr.

XII^e Conférence de l'Union Internationale contra la tuberculose. Rio de Janeiro: Fédération Brésilienne de Sociétés de Tuberculose 1954. Pp. 721.

Klinische Fehldiagnosen. By M. Büger. Stuttgart: Georg Thieme Verlag. 1954. Pp. xvi + 550. Price D.M. 59·40.

Lehrbuch der Tuberkulose des Kindes und des Jugendlichen. By W. Catel. Stuttgart: Georg Thieme Verlag. 1954. Pp. xxiv + 501. 148 illus. Price D.M. 66.

Klinisch-röntgenologische Differentialdiagnostik der Lungenkrankheiten. By Lasar Dünner. Stuttgart: Ferdinand Enke Verlag. 1954. Pp. xi + 274. 334 illus. Price D.M. 49

Das transversale Schichtverfahren. By A. Gebauer and A. Schanen. Stuttgart: Georg Thieme Verlag. 1954. Pp. 313. 469 illus. Price DM 97.50.

REPORTS

ROYAL SANITARY INSTITUTE

The Control of Tuberculosis

The steady decline in the tuberculosis death rate in Britain during recent years was referred to by Dr. W. Hugh Morton, Consultant Chest Physician in Carlisle, and Medical Director of a Mass Radiography Unit in a special area of the Newcastle Regional Hospital Board at a meeting of the Royal Sanitary Institute on November 11, 1954.

In a paper on " Personal Protection of the Individual against Tuberculosis," Dr. Morton said that modern treatment had contributed to the decline of mortality.

" Patients," he added, " are more frequently cured, while those not cured survive for a longer period."

The speaker said that B.C.G. vaccination should be made available to all susceptible individuals regardless of age.

Dr. Morton expressed the view that the ideal position would be for everyone to have a check-up every six months, but present equipment and personnel was, however, inadequate.

He warned his audience that tuberculosis could develop very quickly. " We have seen several cases of quite extensive disease where the individual had a completely normal chest X-ray picture four months beforehand."

Much of the recent criticism of mass radiography schemes would not have occurred if the mass radiography units throughout the country were an integral part of the chest service as was the case in the whole of the Newcastle area.

At the same meeting Carlisle's Medical Officer of Health, Dr. James L. Rennie, gave a paper on the " Environmental Control of Tuberculosis."

Dr. Rennie traced the early history of the disease, and mentioned that the rehousing of tuberculous patients presented a thorny problem.

It would be reasonable to say, however, that local authorities should give a high degree of priority to tuberculous subjects so as to prevent spreading the disease to others.

Concluding, Dr. Rennie said that the public should be educated in the means of preventing tuberculosis. Safeguards should also be instituted to prevent open cases of pulmonary tuberculosis from taking up employment to the danger of others.

CHANGES IN THE CAUSES OF DEATH BETWEEN 1938 AND 1953.

The Registrar-General's Medical Tables Volume of his Annual Review for 1953* gives some interesting figures concerning tuberculosis mortality and cancer of the respiratory system. With regard to tuberculosis mortality, there were under 9,000 deaths for 1953, which was about a third of its level in 1938, and it had declined steadily in each sex since 1947. It had also declined faster in women than in men. On the other hand, mortality from cancer of the respiratory system (over 16,000 deaths) had increased more than two and a half times in men and more than two-thirds in women since 1938.

* The Registrar-General's Statistical Review 1953. Tables Medical. H.M.S.O., price 10s.

However, 1953 was the first year in the ten years ending that year in which there was no increase in mortality from this form of cancer in women.

Mortality from pneumonia (over 20,000 deaths) had declined by about one-third since 1938, rather more for men and less for women; while mortality from bronchitis (over 30,000 deaths) had changed little for men, but declined by nearly a third for women.

BRITAIN'S HEALTH IN 1953

Sir John Charles, Chief Medical Officer of the Ministry of Health, in his Report* for 1953 makes some interesting observations with reference to cancer and tuberculosis.

Cancer.—An increase in deaths due to cancer is largely attributable to the number of men dying of cancer of the lung. This disease predominantly affects men in middle age or later years. The ratio of female to male deaths from lung cancer is 1 to 5½. For the first time in 1953 deaths from lung cancer exceeded those from stomach cancer.

Tuberculosis.—For the fifth year in succession there was a substantial decrease in the number of deaths from tuberculosis—indeed they were only 40 per cent. of what they were in 1948. The number of new cases diagnosed also showed a slight decrease. About one out of every twelve new cases during the year was detected by examination of contacts and one out of every five by radiography.

NOTES AND NOTICES

NAPT FOURTH COMMONWEALTH HEALTH AND TUBERCULOSIS CONFERENCE

The subjects for discussion at the main sessions of the Fourth Commonwealth Health and Tuberculosis Conference to be held by the National Association for the Prevention of Tuberculosis at the Royal Festival Hall, London, from June 21 to 25, 1955, will be as follows:

"The Preventive Outlook Today."
"Child Hygiene and Infection."
"Tuberculosis—A Problem of Different Races."
"Do Death Rates Matter?"
"X-Ray and Tuberculin Surveys—their Meaning and Interpretation."
"Choice of Drugs in Medical and Surgical Treatment of Tuberculosis."
"The Psychology of the Patient and Relatives as a Factor in Successful Treatment."